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THE MENINGES IN LOWER VERTEBRATES COMPARED WITH THOSE IN MAMMALS

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The meninges in lower vertebrates are very different from those in mammals and man.

Though formerly—misled by superficial resemblances—a dura mater, arachnoidea and pia were supposed to exist also in cyclostomes and plagiostomes, at the present time this supposition is maintained only in the "Mikroskopische Anatomie der Wirbeltiere (Heft IV)", published in 1923, by R. Krause, who, however, does not seem to have studied this subject accurately.

In 1884 Sagemehl pointed out that a real arachnoidea does not occur in fishes, and that the wide meshed tissue formerly considered as such really lies between the so-called internal and external (periosteal) dural membrane, and in his study on the comparative anatomy of the meninges, Sterzi [1] emphasized that in cyclostomes and plagiostomes only one undifferentiated meninx is found, which he called meninx primitiva, and considered to be the origin of the dura, arachnoid and pia in higher animals.

It should, however, be emphasized that only the internal dural membrane in higher animals develops from the mesenchymatous blastoma immediately adjacent to the meninx primitiva, the external or periosteal dural membrane originating from the endosteal (or endochondral) connective tissue that in lower vertebrates generally lies at a great distance from the meninx primitiva, and consequently far from the origin of the internal membrane. In my opinion, it is better (Gegenbaur,[2] Poirier

1. Sterzi: Ricerche intorno all' anatomica comparata ed all' ontogenesi delle meningi. Atti del reale instituto veneto di scienze, lettere ed arti, Anno accademico 1900-1901, Vol. 60, pt. 2; Recherches sur l'anatomie comparée et l'ontogénèse des meninges, Arch. ital. de biol. **37,** 1902.

2. Gegenbaur: in Lehrbuch der Anatomie des Menschen, Ed. 6, **2**:441, 1896, speaks of the "von der inneren Lamelle gebildete eigentliche Duralsack des Rückenmarkes."

and Charpy,[3] Testut,[4] Sterzi,[5] and Rauber [6]) not to consider the so-called external or periosteal membrane of the (spinal) dura (which follows all the sinuosities of the bone) as a part of the dura proper, though it fuses with it in the cranial cavity in the adult after an embryonic condition in which it may be distinguished from it.

The distinction of a periosteal and an internal layer in the dura mater spinalis only leads to confusion and to the idea of an ambiguous membrane, which ambiguity disappears by leaving the so-called periosteal dural membrane where it belongs on account of its nature and origin, namely, with the connective tissue of the endochondrium or endosteum.

Concerning the cyclostomes, I found in *Petromyzon fluviatilis* (Fig. 1) the relationships described by Sterzi.

The medulla spinalis is surrounded by a membrane (*B*) in which no differentiation into separate layers is visible. I call this membrane,

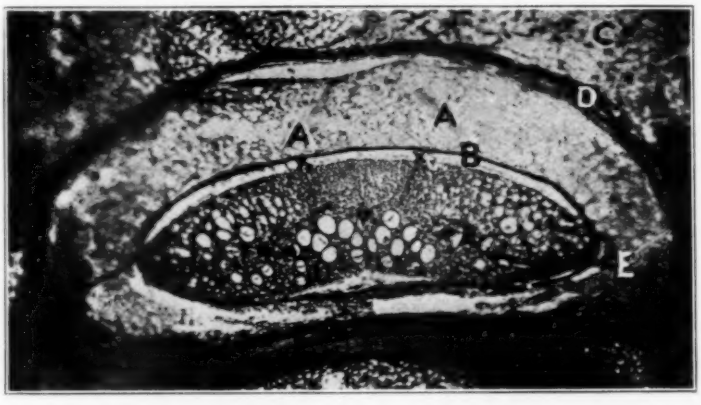

Fig. 1.—Spinal cord of Petromyzon in situ; *x.x*, space between meninx primitiva and cord, caused by retraction; *A*, perimeningeal tissue; *B*, meninx primitiva; *C*, vertebra; *D*, endochondrium; *E*, lateral ligament.

with Sterzi, meninx primitiva. It is continuous with the sheath of the roots. This membrane, which shows lateral ligaments (*E*) extending far laterally into the perimeningeal tissue (Fig. 1), does not yet penetrate with septums into the substance of the spinal cord, so that the membrane is easily detached (*x.x*) from the cord. The nutrition of the

3. Poirier and Charpy: Traité d'anatomie humaine, Paris **3**:107, 1901.

4. Testut speaks of the internal membrane as "dure mère proprement dite" in Traité d'anatomie humaine, Paris, Ed. 6, 1911, p. 1050-1061.

5. Sterzi: Intorno alla divisione della dura madre dell' endocranio, Monitore zoologico italiano, 1902, Vol. 13.

6. Rauber in his Lehrbuch der Anatomie des Menschen **12**:337, 1903, speaks of "Lamina interna oder Dura spinalis in engerem Sinne." A similar opinion is given in Cunningham: Textbook of Anatomy, Ed. 3, 1909, p. 600.

spinal cord has to pass everywhere through the superficial glious layer (limitans superficialis[7]), there being no intramedullary septums and no intramedullary vessels.

Outside this meninx primitiva lies a layer of large cells (*A*), the perimeningeal tissue, which is to be considered as a filling tissue and which reaches as far as the endochondrium (*D*) of the vertebrae (*C*). This perimeningeal tissue consists of round and oval mucous cells.

In some of my preparations spaces occur that look like epidural sinuses, which in human embryos (van Gelderen) are found between the so-called interior layer of the dura and the so-called periosteal layer. I could not, however, find traces of blood here. They are also more or less local spaces that do not spread over a great length. As I could not find any connection with the venae invertebrales, they probably are retraction cavities (caused by the fixation).

The relationships in plagiostomes are not much different. In *Scyllium* (Fig. 2) also I found only one meninx, the meninx primitiva (*D*), in which no differentiation in separate layers is visible. It contains small blood vessels that penetrate with meningeal septums into the spinal cord.

Moreover, the sharks show the four spinal ligaments already described by Sterzi: the rather strongly pronounced lateral ligament (Fig. 2, *A*) and the thinner, scarcely developed dorsal and thicker ventral ligament. Only the lateral ligament extends for some distance through the perimeningeal tissue. The others are merely thickenings of the meninx primitiva. Besides this meninx primitiva which, as in cyclostomes, continues in the root sheath, a large amount of perimeningeal tissue is found (*C*) reaching as far as the endochondrium (*B*), showing much more widely spread meshes than in cyclostomes. Here and there —especially near the endochondrium—it is a little more compact.

Large thin-walled veins (without a muscular coat) are seen in the perimeningeal tissue, on the dorsal (*E*) and on the lateral side. There is no doubt concerning their homology with the so-called epidural veins in mammals and man, although they are relatively much larger and therefore resemble sinuses.[8]

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7. In selachians, meningeal septums with blood vessels grow into the spinal cord, causing a closer relation between the nervous substance and the vascular system. As, however, the limitans gliosa superficialis grows at the same time with those septums, a real penetration of meningeal tissue into the nervous substance itself does not occur. In fact, the septal spaces are to be considered as the fissures in the forebrain, with the difference that they are much smaller and for the greater part filled up with pia tissue, while the arachnoidal cavities in the brain fissures are much wider and go farther downward. They also resemble each other by the fact that the dura remains outside of them, in the brain as well as in the spinal cord.

8. Similar large epidural veins occur in Carnivora, Edentates, Cetacea and Elephas, in which the epidural space still prevails on the arachnoidea.

The relationships in Ganoids (*Acipenser* and *Polyodon*) are similar to those in selachians; so I shall not describe them again.

My researches concerning the relations in the most specialized group of fishes, teleosts, show that there are in this subdivision large differences in meningeal structure that *might* explain the rather different descriptions given in the literature, if the chief and rather different descriptions—those of Sagemehl and Sterzi—were not both partly based on the same material (*Barbus*).

Sterzi [9] presumes that in fishes there is only one meninx, which he calls meninx primitiva, which includes both the dura and the leptomeninges in an undifferentiated state, while Sagemehl [10] distinguishes

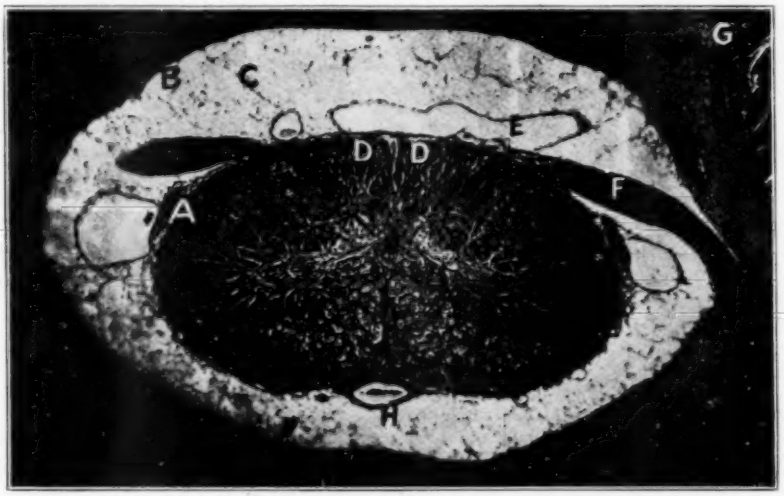

Fig. 2.—Spinal cord of Scyllium canicula in situ; *A*, lateral ligament; *B*, endochondrium; *C*, perimeningeal tissue; *D*, meninx primitiva; *E*, perimeningeal vein; *F*, radix posterior; *G*, vertebra; *H*, arteria vertebralis anterior.

a dural membrane and under it, separated by a fissure, a tissue which is the origin of the pia and the arachnoid—a meninx secundaria as Sterzi calls it in reptiles and birds. This meninx secundaria ("Gefässhaut" of Sagemehl) only in some places shows a differentiation in an inner and outer membrane, which, however, has nothing in common

9. He (and also Sagemehl) remarks that the perimeningeal tissue is mucous in elasmobranchs and ganoids and adipose in teleosts (page 1147). This is not always correct according to my experience. An Acipenser sturio in my collection has, for instance, a large quantity of perimeningeal fat tissue, and I found mucous tissue in several teleosts. It seems that both these tissues are most fit to serve as a buffer substance in a movable enclosure, and that they may replace each other as such.

10. Sagemehl: Beiträge zur vergleichenden Anatomie der Fische. II. Einige Bemerkungen über die Hirnhäute der Knochenfische, Morphol. Jahrb. **9**:457, 1884.

with the differentiation in the arachnoid and the pia. This difference between these authors is the more striking as both, at least partly, examined the same material (*Barbus*).

Personal researches convinced me that the relations in teleosts [11] may be very different. I examined a very small teleost—*Girardinus*—and compared it with a fish which may attain considerable size, *Lophius piscatorius*, and found very different relationships.

In *Girardinus* no differentiation is visible in the meningeal tissue surrounding the spinal cord (and the brain). So here, with Sterzi, one may speak of one meninx primitiva which in this case nearly joins the

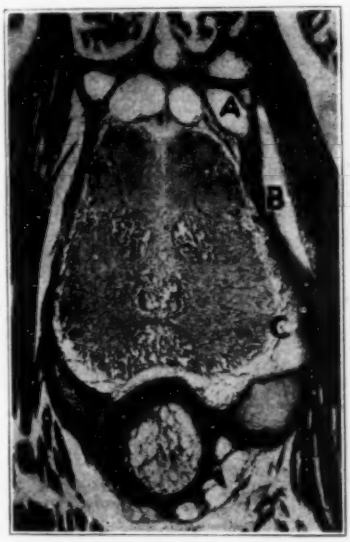

Fig. 3.—Spinal cord of Girardinus (cervical) in situ; *A*, perimeningeal (epidural) sinus; *B*, vertebra; *C*, meninx primitiva.

periosteum, at least laterally, where hardly any perimeningeal tissue is seen between vertebra and meninx (Fig. 3).

Dorsally, where the space between the meninx and the periosteum is wider, there occurs a very thin, exceptionally wide meshed perimeningeal tissue, in which, especially at its dorsal side, large veins appear. The same is found in the area of the oblongata and cranium, with this difference, however, that there is a much larger quantity of perimeningeal tissue in the much larger cranial cavity. Also here no differentiation is

11. For the teleosts Krause's description is practically in accordance with that of Sagemehl. He, however, does not mention Sagemehl's name, and considers the interior layer entirely as a pia mater. That the interior layer contains the origin of both pia and arachnoidea, is not mentioned by Krause.

visible in the meninx primitiva. Consequently, with regard to this animal, Sterzi's description is correct.

In *Lophius piscatorius* other relationships were found. Here also there is a large quantity of wide meshed perimeningeal tissue. The actual meningeal tissue lying under it, however, is very distinct from that in *Girardinus*.

The tissue lying (Fig. 4) immediately under the wide meshed perimeningeal mucous tissue (*B*) forms a fibrous layer (*A*) which in some places is larger than in others, but which may be seen everywhere as a distinct layer. If this layer were separated from the underlying menin-

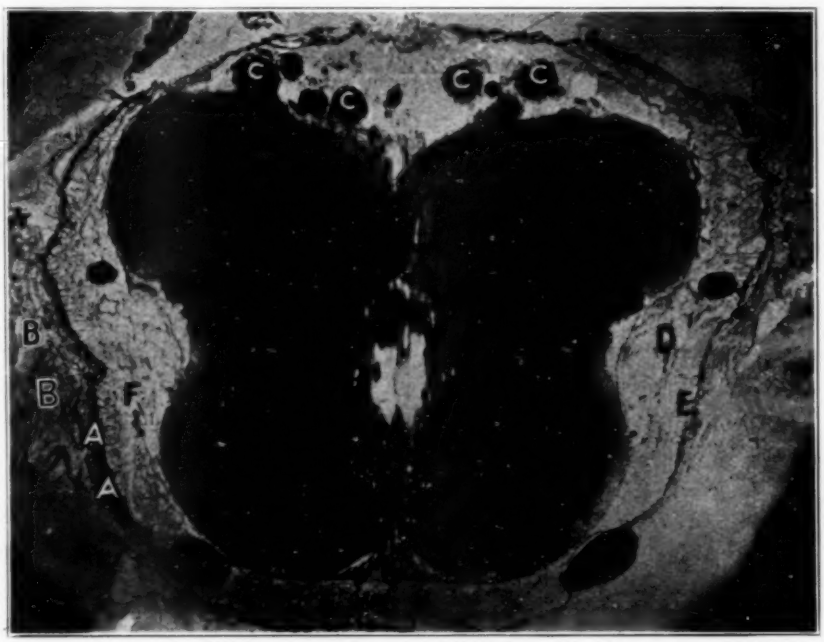

Fig. 4.—Cervical cord of Lophius in the meninges; *A*, dural layer; *B*, perimeningeal tissue; *C*, supramedullary spinal ganglion cells; *D*, interior leptomeningeal layer of the meninx; *E*, exterior leptomeningeal layer of the leptomeninx; *F*, leptomeninx (meninx secundaria).

geal tissue by a continuous split, one would be right in speaking of a well differentiated dura mater. Such a *continuous* split as described by Sagemehl and called "pericerebraler Lymphraum," analogous to the subdural cavity in mammals, I cannot find in *Lophius*. The relations here are similar to those observed by van Gelderen [12] in early human embryos.

12. Van Gelderen: De ontwikkeling der sinus durae matris bij den mensch, Nederl. Tijdschr. v. Geneesk. **68**:2850, 1924; Zur vergleichenden Anatomie der Sinus durae matris, Anat. Anz. **58**, 1924.

This author found that the interior layer of the ectomeninx has become a denser tissue in human embryos of 19.6 mm., contrasting distinctly with the leptomeningeal tissue lying under it, without, however, being separated from it by a fissure, which he did not find in embryos from 25 to 30 mm., but saw first as local dehiscence in an embryo of from 35 to 40 mm.

I found the same condition in *Lophius*, in which I could not perceive a continuous fissure, but only local dehiscences (Fig. 5, *D*) between the dural membrane (Fig. 5, *C*) and the tissue of the meninx secundaria lying under it (Fig. 5, *E*).

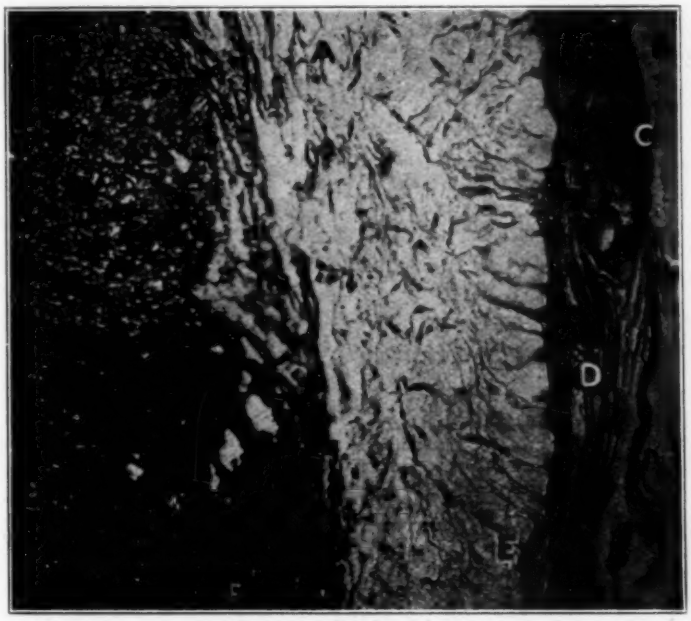

Fig. 5.—Enlarged photograph of the meninges in Lophius; *A*, interior layer of the leptomeninx; *B*, perimeningeal tissue; *C*, dural layer; *D*, fissure; *E*, exterior leptomeningeal layer of the meninx; *F*, medulla spinalis.

Yet I do not hesitate to consider this fibrous membrane lying on the meninx primitiva in *Lophius* as dural tissue, as the fibrous condensation proves that it is developing in the direction of the strongly fibrous dura mater spinalis. If there were a continuous fissure, it would not be correct to speak of a dural condensation of the perimeningeal blastoma but of a real dura mater and a meninx secundaria, as they occur in reptiles.

Concerning the condition of the leptomeningeal part of the meninx, its much more wide-meshed character is striking (Fig. 5). In many places we may distinguish in it an exterior layer *E* from an interior

layer *A* (Fig. 5). In the former, lying directly underneath the mesothelial layer by which it is covered, the cells often stand almost perpendicularly (like palisades) on the external layer of flat cells (Fig. 5), while the meshes of the interior part *A* are much less regular. Another difference is that only the interior layer follows the membrana intima in the septums, and that it contains more small blood vessels in the part that lies immediately on the spinal cord.

Although there is a fairly wide meshed tissue, especially in the palisade part, in my opinion we may not yet compare this with the trabecular tissue of the arachnoid, since real "trabecles," that is, fibrillar threads of connective tissue covered with mesothelial cells, do not occur here. The pseudotrabecles are ramifications of single cells, and consequently might be called monocellular trabecles like those occurring in the wide-meshed reticular tissue of lymph glands. Moreover, in real arachnoid tissue the meshes are much wider and the trabecles far less numerous.

There is another argument in favor of this. In mammals the arachnoid has very wide spaces at the dorsal side of the oblongata on the choroid of the fourth ventricle (cisterna posterior cerebelli), communicating with the ventricle by means of the foramen Magendie (if this occurs). In *Lophius*, however, the wide-meshed leptomeningeal tissue surrounding the whole surface area of the spinal cord on all sides, in the area of the calamus, is dorsally a little less developed, and on the choroid roof still less so, being especially developed at the lateral and ventral sides of the oblongata.[13]

This seems to accord with my opinion that this tissue does not perform an important function in higher animals as a receptacle of the liquor cerebrospinalis externus, but here it performs chiefly the same function as wide-meshed reticular connective tissue does in other places, for instance, in the intestines and lymph glands.

That this differentiation occurred in *Lophius* and not in *Girardinus* may perhaps be due partly to the much larger space of the vertebral canal in the latter. In larger fishes the skull and vertebral canal develop much more than the nervous system itself, and therefore the tissue lying between them also increases considerably. That this increase, which is obvious in the perimeningeal tissue in *Lophius*, does not only concern the perimeningeal tissue (as happens in the cranial cavity of *Girardinus*, which also is much larger than the vertebral canal of this animal) but also in *Lophius* holds good for the leptomeningeal tissue, points to a higher differentiation,[14] to a stage immediately preceding an arachnoidal development.

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13. Ontogenetically Weed, Anat. Rec. **10**:479, 1916, found the meningeal differentiation also occurring first in the basal parts.

14. Girardinus belongs to the Haplomi that are considered to stand at a lower level than the group of the Pediculati, to which Lophius belongs.

Thus far I have given the results of my microscopic research on the meninges in fishes, in which the large quantity of perimeningeal, mucous or adipose tissue stands prominent, its quality of a buffer tissue being of great use to the great flexibility of fishes.[15] We know that traces of a thin perimeningeal adipose tissue still occur in man, in the space between the actual dural membrane and the endosteum of the vertebrae, while it disappears in the cranial cavity, which is much less subject to changes in form.[16]

The comparison between fishes and man, however, demands a further explanation as far as the development of the arachnoid spaces and the liquor cerebrospinalis externus is concerned.

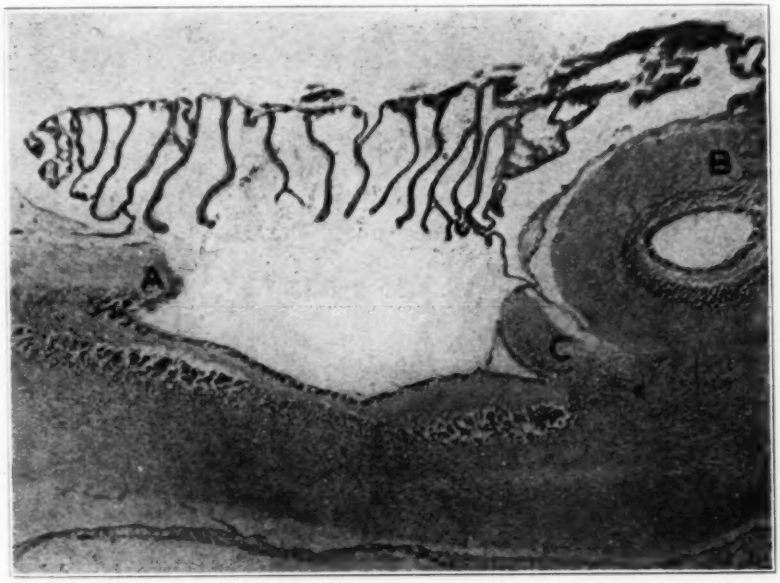

Fig. 6.—Fourth ventricle with high choroidal roof in Petromyzon fluviatilis, sagittal; *A*, calamus; *B*, tectum mesencephali; *C*, cerebellum.

There is no doubt that the lowest vertebrates, such as cyclostomes, plagiostomes, ganoids and teleosts, do not have actual arachnoidal cavities and consequently no liquor cerebrospinalis externus, which in mammals fills the subarachnoidal cavities, and the total volume of which in man considerably surpasses the volume of the liquor cerebrospinalis internus (ventricular fluid).

15. The fact that the movements made by fishes in swimming are chiefly lateral may perhaps explain the preponderance in the size and development of the lateral ligaments.

16. Compare also Poirier and Charpy.

Together with the absence of liquor cerebrospinalis externus, we see the striking fact that the liquor cerebrospinalis internus—the ventricular liquor—is not seldom richly developed in lower fishes.

The relatively large volume of liquor cerebrospinalis internus is not only proved by the wide ventricles in plagiostomes (especially sharks) and cyclostomes, but also by the fact that where these ventricles are covered at the surface by a choroidal membrane, that generally bulges outward very considerably, as is shown, for example, in the fourth ventricle and the roof of the midbrain of *Petromyzon* (Fig. 6). Also other primitive fishes—for instance, *Ceratodus* (v. d. Horst [17])—have similar protruding choroid membranes, and with some fishes (*Lepidosteus* and *Amia*), the choroid roof of the third ventricle (the so-called

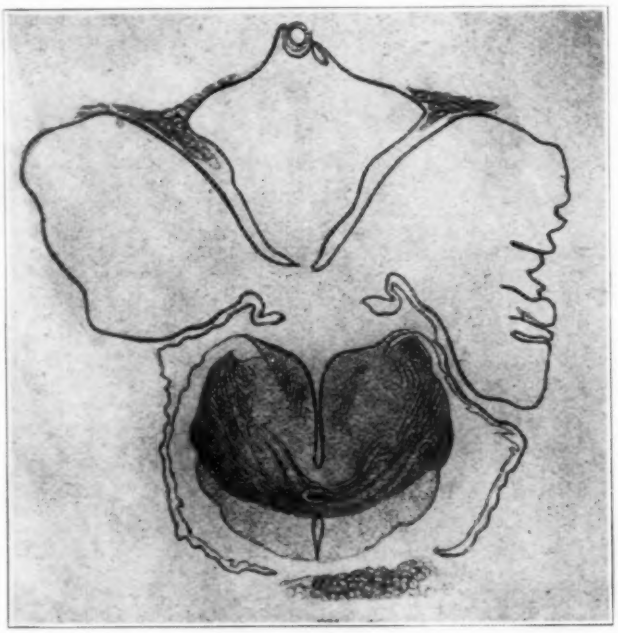

Fig. 7.—Cross section through the frontal part of the thalamus with large recessus dorsalis, laterales and ventrales of the choroid of the third ventricle in Lepidosteus osseus.

parencephalon) even evaginates in such a degree to all sides that choroidal sacs are formed filled with liquor internus, extending outside along the brain wall, far frontally as well as caudally (Fig. 7).

It is evident from all this that the liquor internus has a relatively large volume in many lower animals, in strong contrast to the absence of arachnoidal cavities and liquor externus.

17. Holmgren and Van der Horst: Contribution to the Morphology of the Brain of Ceratodus, Acta Zool., 1925.

It is interesting that in higher animals, especially mammals—in which the arachnoidal cavities with their liquor externus develop markedly,[18] and at last surpass the volume of the ventricular liquor—the choroidal membranes are of no more use as sacs, but, with few exceptions,[19] grow inward into the ventricles as ventricular draining organs.

In my handbook of comparative anatomy of the brain (Part 2, page 820), I have stated that the coincidence of the accumulation of arachnoidal fluid on one hand and the growing of the choroid membranes into the ventricles on the other (secreting fluid into and at the same time draining the ventricles) is not accidental. It is certain that most of the liquor externus does not originate at the place where it later occurs, but—certainly for the greater part—originates from the ventricular fluid, which diffuses through the choroidal membranes (with or—in most cases—without assistance of the foramina of Luschka or Magendie).[20]

This origin of liquor externus certainly is the most important one, although it may be added that in some places a slight diffusion of ventricular liquor takes place through the ependyma of the ventricles, and arrives into the Virchow-Robin spaces around the vessels of the brain and so into the arachnoid cavities.

In connection with this it is interesting that Dr. Frederikse in the Institute for Brain Research could prove the existence of so-called "Kittsubstanz" (which also is present between choroid cells and between intestinal epithelium) between the ependyma cells of the ventricles in the lizard (not yet published).

In view of the fact that the greater part of the liquor arachnoidalis originates in the diffusion of ventricular fluid through the choroid, it is not strange that the formation of the arachnoidal sacs in mammals occurs simultaneously with a greater draining action and inversion of the choroid.

Of both choroidal functions, namely, the secretion of fluid into the ventricle[21] at one side, and at the other the draining of ventricular fluid, the first mentioned function occurs first, and this explains the

18. Smaller arachnoidal cavities occur in birds, as Hansen Pruss showed by injections (J. Comp. Neurol. **36,** 1923).

19. The recessus laterales of the oblongata.

20. These foramina are seen for the first time in mammals and do not occur in all mammals. They are sometimes even absent in man.

21. The ependyma also takes some part in this function at least in some places (for instance, in the infundibulum). As shown in my book **2**:821, Fig. 437, and page 853, Fig. 455 *A* and *B* and the communications of Wislocki and Putnam. Note on the Anatomy of the Areae Postremae, Anat. Rec. **19,** 1920; Further Observations on the Anatomy and Physiology of the Areae Postremae, ibid. **27,** 1924.

strong protrusion of the choroidal sacs in lower fishes as well as the absence of proper arachnoidal cavities in these animals.

That this process repeats itself in the same order in embryologic development is shown by the researches of Lewis Weed,[22] who proved that, while the ventricular fluid appears in embryos in the first stage of ventricular development, the liquor externus is found in the arachnoidal cavities of the pig for the first time in an embryo of 14 mm.

A few words may be added concerning the meninges in reptiles, birds and mammals. I shall be brief, since the relations in adults of these classes are more generally known than those in the lower classes, although scarcely any good illustrations are given in the literature.

In reptiles we find (as indicated by some *Amphibia*) that the dura is fairly well indicated and separated from the underlying leptomeninx by a small subdural space. The leptomeninx itself may still be considered a meninx secundaria in the sense of Sterzi, i. e., differentiation

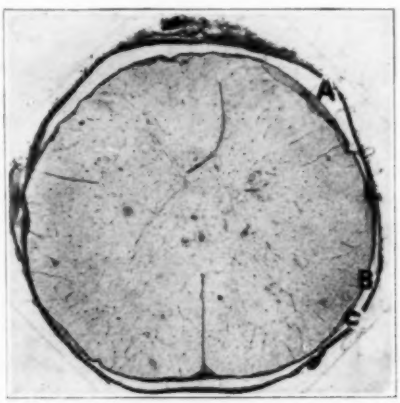

Fig. 8.—The well developed dura meninx and subdural space in Athena (the owl); *A*, subdural space; *B*, leptomeninx; *C*, dura mater.

in the pia and in the arachnoid has not yet occurred, and there are consequently no arachnoidal cavities containing liquor spinalis externus. Outside the dura there is a large amount of epidural tissue lying between the dura and the endosteum of the vertebrae, showing large epimeningeal veins with thin walls consisting only of endothelium, as is usual with epidural veins and sinuses.

In birds the dura is more differentiated (Fig. 8, *C*) the subdural space being more evident. There is also some differentiation in the underlying meninx secundaria, an indication of a beginning development of arachnoidal spaces, which, although still small, allow injected fluid to spread over a large extent from the cervical into the thoracic

22. Weed, Lewis: Development of the Cerebrospinal Spaces in Pig and Man, Contributions to Embryology, Carnegie Institution **5**, 1917.

region, as was shown by Hansen Pruss. I shall not discuss the peculiar condition of the leptomeningeal tissue in the sinus lumbosacralis, consisting largely of vesicular cells derived from the leptomeninx and (around the central canal) some glia cells. Pruss described it recently and I have dealt with its histologic constituents a little more elaborately in the "Publications of the Peking Union Medical College" (1924).

I take one illustration from this treatise to give the reader an idea of the peculiar tissue relations in this region in birds, in which the central canal (*A*), the ependyma of which has only a few atrophied offshoots, lies in the leptomeningeal derivative that surrounds it (*D*), mixed with a few glia cells (*B*), near the canal. (*EE* is the membrana limitans gliosa.)

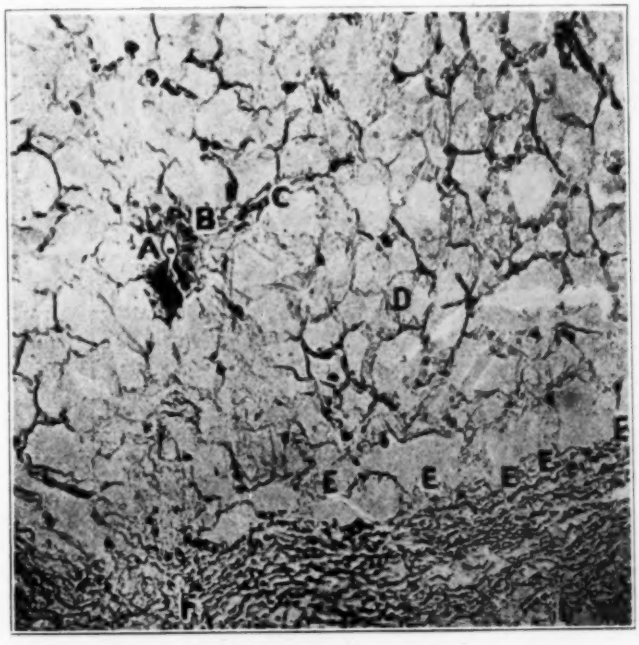

Fig. 9.—Lumbosacral sinus of the Chinese chick. Pericanalicular (subependymal) glia cells approaching a blood capillary. The vacuolized character of the leptomeningeal cells is very clear; *A*, central canal; *B*, group of glia cells; *C*, capillary; *D*, vacuolized cells of leptomeninx; *E*, nuclei of the membrana intima piae; *F*, nervous tissue.

To enable the reader to compare the relationships in mammals with those in fishes, I present two photomicrographs of sections through the vertebral canal of a cat, taken a few days after birth (Figs. 10 and 11). It is important to identify the amount of epidural fat (*B*) lying between the dura and the endosteum of the vertebrae and the presence of large epidural veins in this tissue (Fig 10, *A*) of the same character as the perimeningeal veins in sharks (Fig. 2). In

Figure 11 of the same animal it is seen that the dura continues in the perineurium of the roots (the arachnoidal tissue which is hardly seen in most places in the illustration, the whole arachnoidal region looking like one large space), and enters inside the roots, as Key and Retzius demonstrated by injections, and as was confirmed by Lewis Weed, who could even demonstrate villi-like growth of these arachnoidal offshoots in the roots, thus showing the possibility of vacuation of spinal fluid by the roots.

I shall not discuss the embryonic origin of the meninges, which I did not investigate. As may be known, Gegenbaur believed that the dura, together with the endosteum of the vertebrae, forms a system of its own, the primitive ectomeninx, while the two leptomeningeal membranes arise in close topographical connection with the spinal cord.

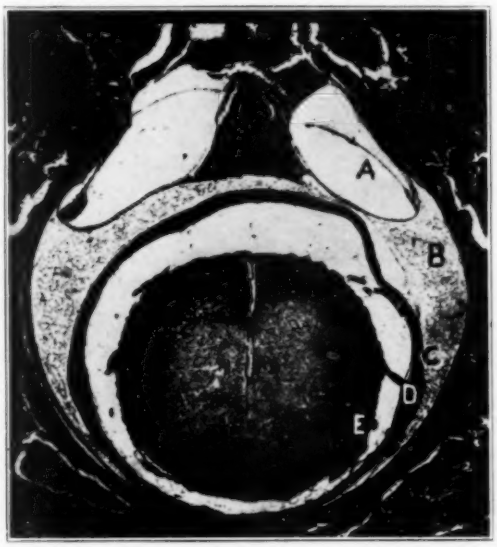

Fig. 10.—Spinal cord in situ. Cat, neonatus; *A*, epimeningeal veins; *B*, perimeningeal adipose tissue; *C*, dura; *D*, ligamentum denticulatum; *E*, spinal cord.

On the other hand, Sterzi defended the origin of all the meninges, including the dura, from the meninx primitiva closely surrounding the spinal cord. The first opinion is also defended by van Gelderen and finds strong and interesting confirmation in the recent researches of Harvey and Burr,[23] who showed that in pig and chick embryos the leptomeninx tissue arises from the neural crest, thus showing that there is a definite histogenic difference between the dura and the leptomeninx, the latter developing from the neural crest cells, the former

23. An Experimental Study of the Origin of the Meninges, Proc. Soc. Exper. Biol. & Med. 1924, Vol. 22.

probably from the mesenchyme. In view of the fact that even some gill cartilage may develop from the neural crest, according to some embryologists,[24] this finding is not so astonishing. Van Gelderen, however, could prove that the fibrous membrane surrounding the leptomeninx (the dural layer in Figs. 4 and 5) in *Lophius* originates embryologically from the same primitive membrane from which the leptomeninx itself originates. Therefore the principle of convergence may be applied here, i. e., that a primitive dural membrane—or a membrane structurally and topographically almost similar to the primitive dural sheath—under certain circumstances may develop with the leptomeninx. The local dehiscence between this membrane and the leptomeninx in *Lophius*, and its position interior both to the epimeningeal fat tissue and epimeningeal veins, also its more fibrous character and its continuation in the root sheaths, indicate a beginning dura differentiation. So we have

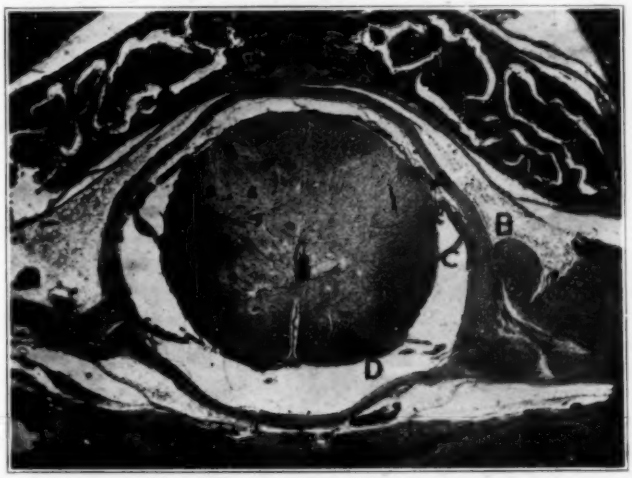

Fig. 11.—Spinal cord in situ. Cat, neonatus; *A*, dura; *B*, perimeningeal adipose tissue; *C*, ligamentum denticulatum; *D*, arachnoidal region.

to accept in *Lophius* that either in a very young stage the *perineural mesenchyme* links up closely with the neural crest derivatives,[25] or that the manner of differentiation is different from that in mammals in that the primitive meninx gives rise to both the leptomeninx and the dura. In view of the statement made above that the neural crest may even supply cells for the cartilage of gill arches, this does not seem impossible.

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24. Landacre: The Fate of the Neural Crest, J. Comp. Neurol. **33,** 1921.

25. According to van Gelderen's previous researches in human embryos, a continuous subdural space is still lacking, there being a tissue continuity between ectomeninx and endomeninx. Local dehiscence later introduces the formation of a continuous fissure which is thus secondarily acquired.

The third possibility, that the more fibrous membrane surrounding the leptomeninx in *Lophius* and lying interior to the perimeningeal fat tissue and perimeningeal veins may not be compared with a developing dural membrane seems rather artificial, since its structure and its topographic relations to the externally adjacent tissue are principally the same as that of the true dura (Figs. 10 and 11). Moreover, according to van Gelderen's researches in man, a continuity of tissue exists between the anlage of the dura and the anlage of the endomeninx (leptomeninx).

As a whole, the most probable relation seems to be that the primitive leptomeninx is independent in its origin from the dural membrane, and that the real dura develops from the mesenchymatous blastoma immediately surrounding the leptomeninx, i. e., from the perimeningeal tissue but not from the endosteum of the vertebrae from which only the so-called external or periosteal lamella arises, that, however, should not be considered as a dural lamella.

The comparative anatomy of this much neglected field, in connection with the late development of circumspinal fluid and arachnoidal spaces in the series of vertebrates, may be also of some interest to the physiologist and to the clinician.

ENCEPHALITIS PERIAXIALIS DIFFUSA OF SCHILDER

REPORT OF A CASE *

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Ever since Schilder's [1] description in 1912 of a peculiar clinical and pathologic syndrome which he called encephalitis periaxialis diffusa, various continental observers have reported isolated examples of this rare and interesting disease. Recently, Collier and Greenfield [2] of England and Bouman [3] of Holland reported four instances with thorough clinical and pathologic investigation. Up to date, thirty-two observations of encephalitis periaxialis diffusa have been reported, and the reader is referred to the later articles, especially Bouman's, for detailed analysis of thirty of these cases.

A study of our case and the literature confirms the belief that we are dealing with a syndrome having a fairly typical course and pathology, which frequently should be capable of diagnosis during life. It may be pointed out that Collier recognized his second case during the patient's life. These English writers describe the disease as:

> A malady usually occurring in children and young subjects with no tangible causal factors or antecedents. The onset is a few days, the course progressive, with some remissions, to a fatal issue; the duration from a few months to three years. The chief early sign is cerebral blindness which becomes complete, to which are added mental reduction and increasing spastic paralysis. Unsteadiness from parietal involvement and deafness from temporal involvement may be conspicuous. The amentia increases and passes into coma which terminates the illness. The condition, usually bilateral, may commence on one side or may be confined to one side.

REPORT OF A CASE

History.—M. L., a boy, aged 9, American born of Russian Jewish parentage, the third of four children, was born at full term, without the use of instruments. There was no consanguinity in the family history, which otherwise was also without significance. The boy had diphtheria at the age of 3; measles at 5, and

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* Read by title at the Fifty-First Annual Meeting of the American Neurological Association, Washington, D. C., May, 1925.

* From the Second Division of the New York Neurological Institute.

1. P. Schilder: Zur Kenntnis der sog. diffusen Sklerose (über Encephalitis periaxialis diffusa), Ztschr. f. d. ges. Neurol. u. Psychiat. **10**:1, 1912.

2. Collier and Greenfield: Encephalitis Periaxialis of Schilder, Brain **47**: 489-519 (Dec.) 1924.

3. Bouman, L.: Encephalitis Periaxialis Diffusa, Brain **47**:453-488 (Dec.) 1924.

tonsillectomy was performed at the age of 7. The patient was considered bright at school until November, 1920, when his teacher noted that he had become irritable and fidgety. At that time also intention tremor of both hands developed, with defective memory and inability to read or do school work. He was demoted two classes. In December, 1920, to increasing difficulty in vision were added deafness and weakness of the right lower extremity, the right leg and foot being dragged in walking. These symptoms increased in intensity until May 16, 1921, when there occurred a generalized tonic and clonic convulsion lasting two and one half hours, which was followed by drooling of saliva, complete disorientation, difficulty in talking and weakness of the right side of the body. A few days after the convulsion it was noted that he could not walk, that he was apathetic, and that the impairment of sight was more marked. He also complained of headache at that time. May 17, 1921, he was admitted to Mt. Sinai Hospital, New York, in the service of Dr. Bernard Sachs. Just after admission, there was a generalized convulsion with involuntary urination. The boy remained at this hospital until June 24, 1921.

Physical Examination.—On admission to Mt. Sinai Hospital, examination revealed: pupils equal and reacting promptly to light and in accommodation; fields and fundi normal; corneal reflexes present, no ocular palsies and no nystagmus. There was slight right facial weakness, more of the lower part, probably thalamic in type. Hearing was normal. The patient apparently perceived odors. The tongue and palate were normal. There seemed to be a sensory aphasia. There was ataxia of the right side which was more marked in the upper extremity. The gait was hemiplegic on the right with a broad base and shuffling of both feet. The upper deep reflexes were lively, and the right knee and ankle reflexes were greater than the left. The right abdominal reflexes were diminished and easily exhausted; the left were not very active; the right cremasteric reflex was less active than the left. There was no clonus, but a Babinski sign was present on the right. Bilateral hypesthesia was present, but deep sensibility was apparently normal throughout. Percussion tenderness was noticed on the left side of the skull. Mental reactions were apathetic, and the patient did not respond promptly to questions; it was a problem whether or not he understood. He carried out commands only after numerous repetitions of the orders.

Course.—On May 20, right hemianopia was observed, but there was no accompanying hemianesthesia. A cerebellar ataxia with intention tremor of the hands was noted. A bilateral Babinski sign, greater on the right, was found at this time.

On May 21, he had visual hallucinations ("saw water all around him").

On May 24, the middle ear and hearing were normal. There was no spontaneous nystagmus; it was impossible to test past pointing; the patient did not fall definitely to one side or the other. The caloric reaction was positive and prompt, thirty-five seconds on both sides. No involvement of either auditory nerve could be determined.

On June 3, there were right hemiplegia, right hemiasynergia and intention tremor of the right hand. The visual fields showed a right hemianopia. The patient correctly described objects at a distance of 8 feet (245 cm.). The fundi were normal. The spinal fluid was clear and contained no cells; the globulin and Fehling tests and the Wassermann reaction were negative; the fluid was sterile.

On June 6, at 11 p. m., the boy suddenly became maniacal, screamed and attempted to climb out of bed, saying someone was going to eat him. There

was no evidence of a convulsion. The following morning he had a similar attack. At other times, he screamed and imagined that he was in an aeroplane.

On June 13, he appeared brighter and more docile. A convergent squint with weakness of the right side of the face and ptosis of the right lid were noted. The right hand showed choreo-athetoid movements.

On June 21, a right hemihypesthesia was present. While at the hospital, the body temperature ranged from 99.2 to 99.4 F. with an occasional rise to 100. The pulse averaged 92; respiration 20. Roentgenograms of the skull were negative. The boy was discharged from Mt. Sinai Hospital, June 20, 1921.

After leaving the hospital, spasticity appeared in the left upper extremity, speech difficulty increased, and dysphagia developed. By Nov. 21, 1921, the boy had become completely inarticulate, and swallowing was so difficult that he could be fed only liquids.

Reexamination.—On Dec. 28, 1921, thirteen months after the onset, the patient was admitted to the New York Neurological Institute. At that time examination showed: smell could not be tested; pupils were dilated but active to light and in accommodation; fundi were normal; the visual fields could not be determined; ocular movements were normal; there was no nystagmus; light perception was absent in both eyes. There were anarthria and great difficulty in swallowing; the tongue could not be protruded. The other cranial nerves could not be tested. Both upper extremities were spastic; the right more than the left; there was no localized atrophy; the hands were clenched, the fingers flexed over the thumbs, which were abducted into the palms; the elbows were extended and the shoulders adducted. Both lower extremities were spastic, the right more than the left; extension was noted at all joints. The patient was unable to walk or stand; the feet were held in the equinovarus position. The head was retracted, the trunk somewhat opisthotonic. *The attitude was one of decerebrate rigidity.* The ulnar, radial, triceps and biceps reflexes were brisk, the right more so than the left; there was a bilateral Hoffman reflex; the abdominal, epigastric and cremasteric reflexes were absent; the knee and ankle reflexes were overactive; bilateral Babinski sign and ankle clonus were present. Sensory examination could not be carried out owing to lack of cooperation. There was spontaneous, unmotivated grimacing, with groaning and crying. Incontinence of urine and feces occurred. The patient was much emaciated. While in the hospital, the temperature ranged from 98 to 100 F., with an occasional rise to 101 F. Roentgenograms of the skull were negative. The spinal fluid was clear and not under increased pressure; no cells nor globulin were noted; the Wassermann reaction was negative, and no tubercle bacilli were found. Blood count revealed: hemoglobin, 80 per cent.; color index, 0.8; red cells, 5,000,000 and white cells, 8,000 per cubic millimeter; neutrophils, 68; small lymphocytes, 28; transitional cells, 4 per cent. There was no change in the morphology of the red cells.

Subsequent Course.—About one week after admission to the hospital, the condition seemed to improve somewhat; the patient seemed brighter, could be fed more easily, grimaced and groaned less. However, this improvement lasted only a few days, after which progressive weakness set it.

On March 15, 1922, the temperature began to rise, the pulse rate increased and respiration became more rapid.

Death occurred on March 16, 1922, sixteen months after the onset of the illness, the temperature rising to 105.5 F., the pulse rate to 138 and the respiration to 30.

Pathologic Report.—The meninges were of normal appearance. There was some convolutional atrophy in the parietal and occipital regions of both hemispheres, with a normal appearance of the frontal lobes.

The brain, sliced in vertical sections from the occipital poles forward to the frontal lobes, showed a bilateral lesion of the white matter, commencing in the occipital region and extending forward as far as the anterior portion of the corpus striatum. The temporal lobes were not so much affected as the occipital and parietal lobes, and the extreme tips of the occipital lobes were less affected than the sections farther forward. The corpus callosum was involved in the degeneration, as was also the internal capsule to some extent. Grossly, the brain stem and the cerebellum appeared normal, although the detailed microscopic study of the full extent of the lesion has not yet been completed.

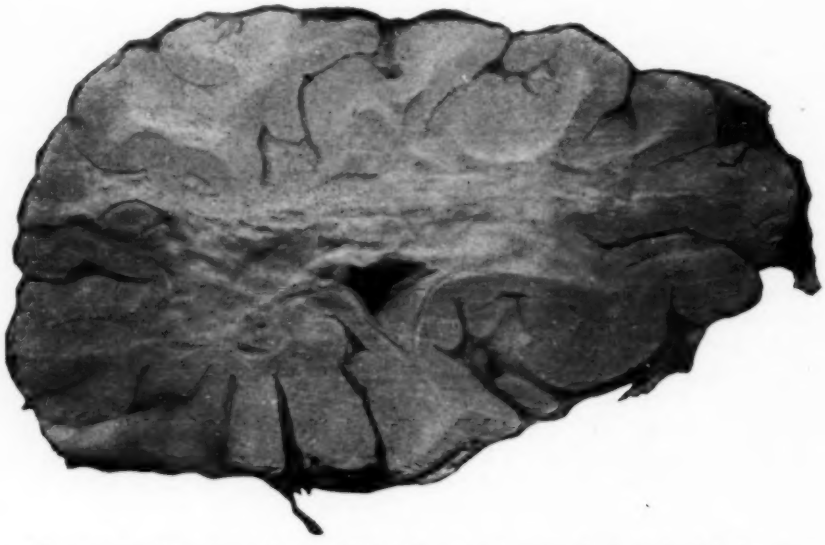

Fig. 1.—Section through occipital lobe showing marked periaxial degeneration of white matter.

The accompanying illustrations give an idea of the appearance and extent of the degenerated white matter of the brain. The areas affected were rough, gelatinous and of a slightly darker gray color than the normal white matter. A narrow, white band, representing the normally myelinated portion of the neurons, could be seen immediately beneath the gray matter of the cortex. Although the gray matter of the brain is not usually much affected by this disease process, there was some thinning of the cortex over the affected regions, and the cortex was less vascular here than in the frontal region.

The ventricles and the choroid plexuses appeared normal.

Figure 5 shows the characteristic demyelination of neurons brought about by this disease. The neurons are completely denuded of myelin, except for a short distance immediately below the cortical gray matter. Sections stained for axis cylinders by Bielschowsky's method showed that these were relatively better and longer preserved than the myelin sheaths, but they were not normal, even when visible, in the demyelinated areas.

Sections stained with scarlet red and osmic acid showed a notable collection of fat droplets beneath the cortical gray matter. The osmic acid stain also showed numerous granular corpuscles (usually not large ones) in the degenerated areas, especially collected about the numerous blood vessels in the white matter.

The hematoxylin-eosin sections showed well the so-called "large globoid cells" which appear to be a prominent feature in the cellular pathology of Schilder's disease. A collection of these cells is seen in Figure 9 clustered about a small vessel and mingled with a number of cells of quite different types. These large globoid cells were round, usually with a single, occasionally a double, nucleus, as a rule located at the periphery of the cell. The cytoplasm appeared slightly granular and stained pale orange red, both in the

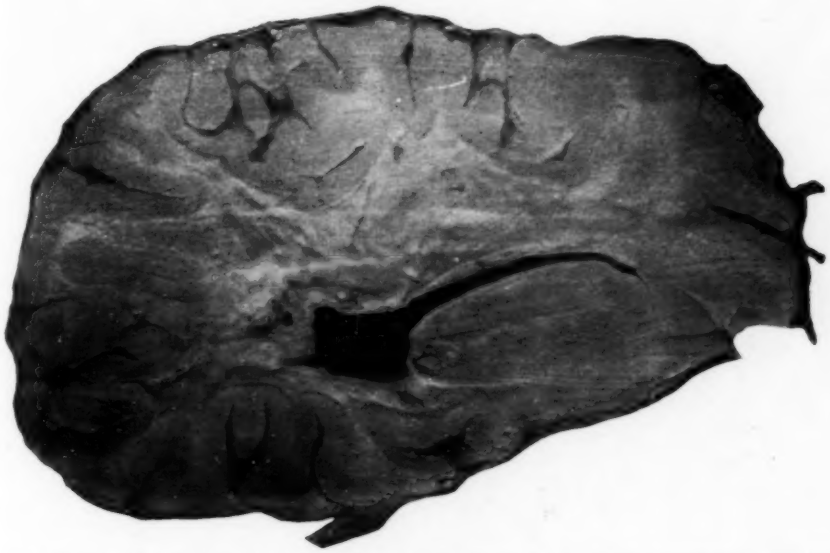

Fig. 2.—Vertical section of the brain through the lateral ventricle showing extensive degeneration of white matter.

hematoxylin-eosin sections and in the frozen sections stained with scarlet red and hematoxylin. These cells were found in and about blood vessels and also in little nests surrounded by proliferated neuroglia fibers. They somewhat resembled endothelial cells.

Frozen sections stained with Victoria blue gave an excellent picture of the neuroglia. The fibers were dense and spider cells were numerous in the demyelinated regions. We did not find spider cells within the cortical gray matter, however, as was described by Collier and Greenfield.

Sections stained by Nissl's method showed slight changes in the cortical cells of the parietal lobes; the cells here were shrunken with empty spaces about them; whereas those of the frontal lobes did not present this appearance. Some chromatolysis was also present.

Because of the possibility of intravitam diagnosis, it becomes necessary to review and evaluate the signs and symptoms with respect to

frequency and diagnostic value. Schilder [4] and Urechia, Mihalescu and Elekes [5] have recently described two cases, which, with ours, bring the number to thirty-three. An analysis of these cases follows.

In the thirty-three cases, the average age was 20 years, the youngest patient being a child aged 1 year, the oldest a woman aged 43. The incidence in decades is: from 1 to 10 years, eleven cases; 11 to 20 years, six cases; 21 to 30 years, seven cases; 31 to 40 years, seven cases; 41 to 50 years, two cases. Thus, the first two decades claim more than one half. There were twenty males and thirteen females.

The average duration as computed for twenty-eight cases was fourteen months. This is exclusive of Krabbe's case of five day's duration

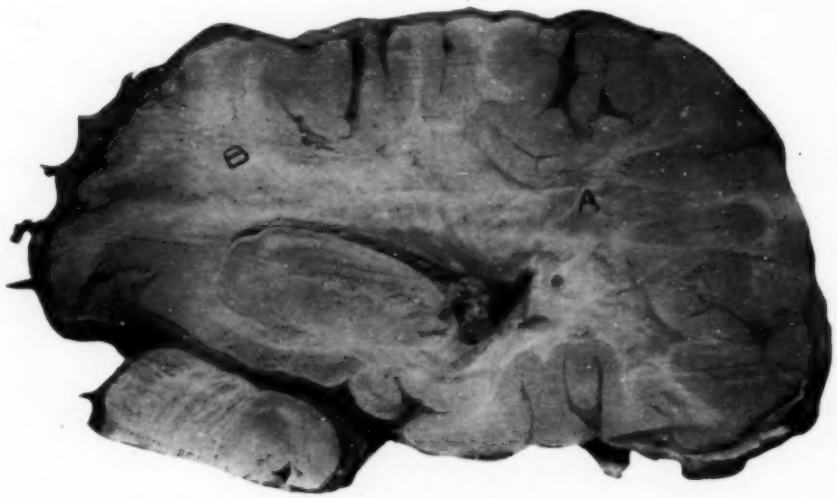

Fig. 3.—Vertical section of the brain showing degeneration still well marked at *A* but beginning to give place to more normal white matter at *B*.

and the one of Marie and Foix lasting ten years. The latter presented the only instance of a remission which lasted nine years. The disease invariably progressed to a fatal termination.

SYMPTOMS

The most common early symptom was apathy, which was noted in sixteen of the thirty-three cases (48 per cent.). It was a forerunner of the extreme deterioration or amentia which constantly appeared toward the end. Psychic disturbances (depression, halluci-

4. Schilder, P.: Die Encephalitis periaxialis diffusa, Arch. f. Psychiat. **71,** No. 3, 4, 1924.

5. Urechia, G. I.; Mihalescu, S., and Elekes, N.: L'Encéphalite periaxiale Diffuse Type Schilder, Encéphale **19**:617 (Dec.) 1924.

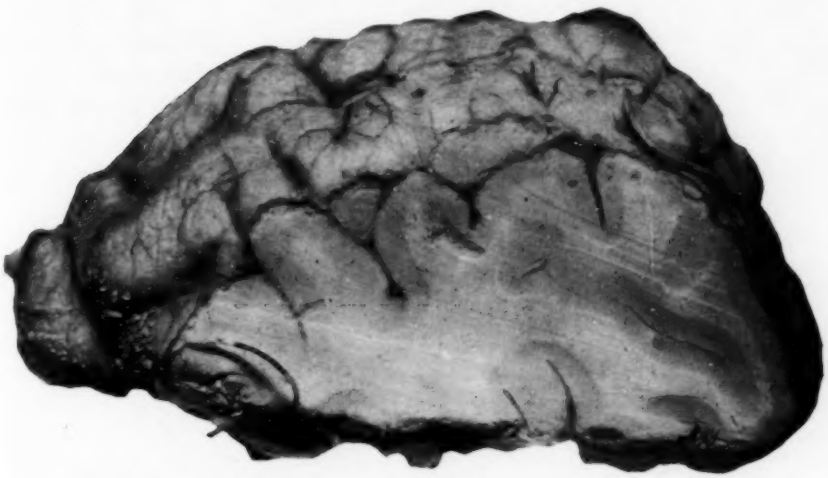

Fig. 4.—Vertical section through tip of frontal lobe showing no evidence grossly of the degenerative process.

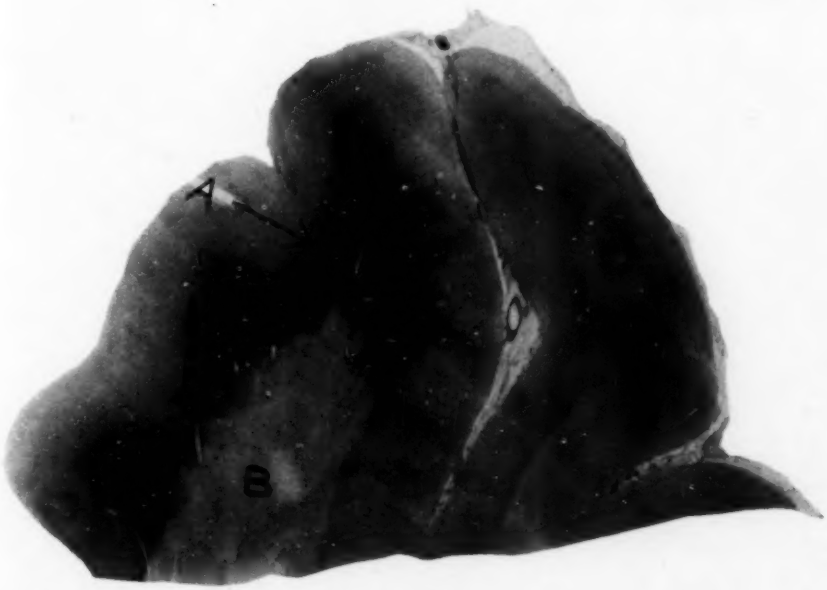

Fig. 5.—A section from the parietal lobe. *A*, narrow zone of normally stained myelin sheaths immediately beneath the cortical gray matter; *B*, degenerated region of white matter where axons are completely demyelinated. (Loyez' method for myelin sheaths.)

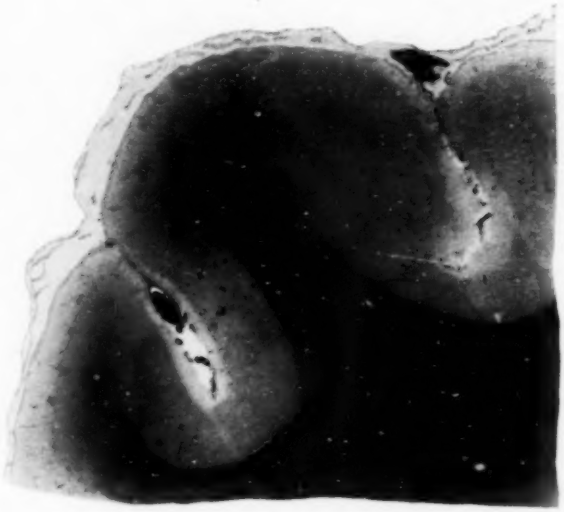

Fig. 6.—A section from the frontal lobe, showing the normally staining myelin throughout. (Loyez' stain.) Compare vascularity of gray matter in Fig. 6 with much less vascularity in Fig. 5.

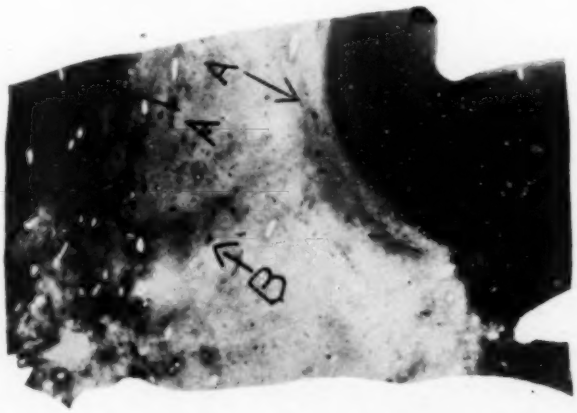

Fig. 7.—A section from the parietal lobe. *A*, zone of fat droplets beneath the cortical gray matter; *B*, demyelinated region with numerous blood vessels surrounded by fat laden cells. (Frozen section: scarlet red and hematoxylin stain.)

nations and delusions, euphoria, excitement and noisy behavior) occurred in eleven cases (33 per cent.). Vomiting was noted in six cases (20 per cent.). Incontinence was present in eleven cases (33 per cent.) in the earlier stages, and was quite constant toward the end.

Ocular Disturbances.—Disorders of vision were most important. In fifteen cases, vision could not be tested or no reference to it was made. Unilateral hemianopia was noted in five cases; five patients were totally blind; vision was diminished or the fields were contracted in six cases; vision was normal in only one case. The optic disks were not commented on in nine cases; they were normal in fourteen; bilateral neuritis or papilledema with swelling up to 3 and 4 diopters occurred in eight,

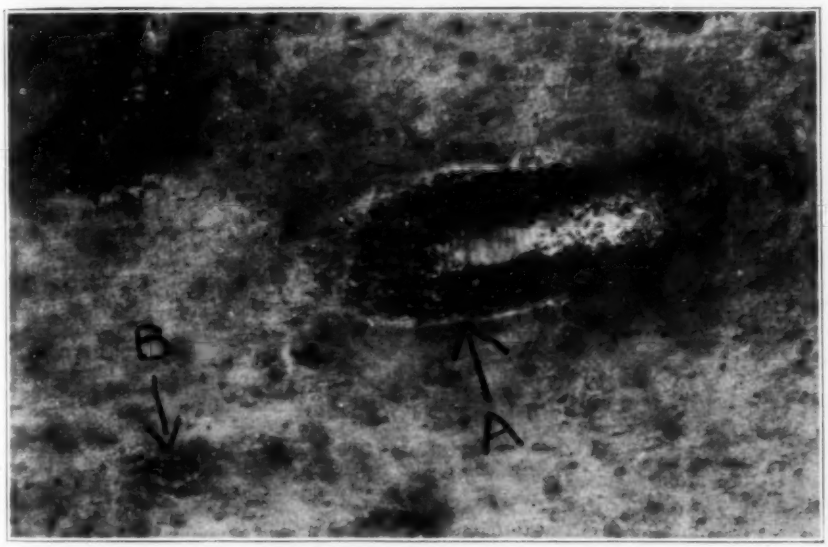

Fig. 8.—Greater magnification of demyelinated area shown at *B* in Figure 7, to show: *A*, the perivascular cuffing of cells, many of them being granular corpuscles laden with fat; *B*, small nest of "large globoid cells." (Frozen section stained with scarlet red and hematoxylin.)

and unilateral optic neuritis occurred in three. The presence of bilateral neuritis in 25 per cent. of the cases, especially if combined with headache and vomiting, suggests the possibility of an erroneous diagnosis of brain tumor. "But the *mild* nature of the optic disc changes and their non-progression to the more intense degree of papillitis in the presence of signs of rapidly increasing and widely-spread cerebral destruction are important in making a distinction between the two conditions. Especially indicative in this connection is the bilateral affection of the hemispheres from the first in so many of the cases, which, in the absence of definite indications of brain-stem affection, is very much against the

diagnosis of tumour" (Collier and Greenfield). Nevertheless, the question of brain tumor cannot be dismissed too lightly. In his third and most recent case, Schilder thought he was dealing with a left frontal neoplasm. A summary of this case illustrates the difficulties of diagnosis in certain instances.

One month after an attack of "grip," a woman, aged 37, lost the sense of smell on the left side; urinary incontinence, frontal headache and weakness followed. Neurologically she showed right pyramidal paresis, left anosmia, uncertain gait with retropulsion, atypical bilateral tremor of the hands, greater in the right than in the left, slowness and lack of spontaneity of movement and bilateral papilledema. Schilder stresses the apraxia of lid closure. The patient was unable to shut her eyelids; she wrinkled her forehead with great

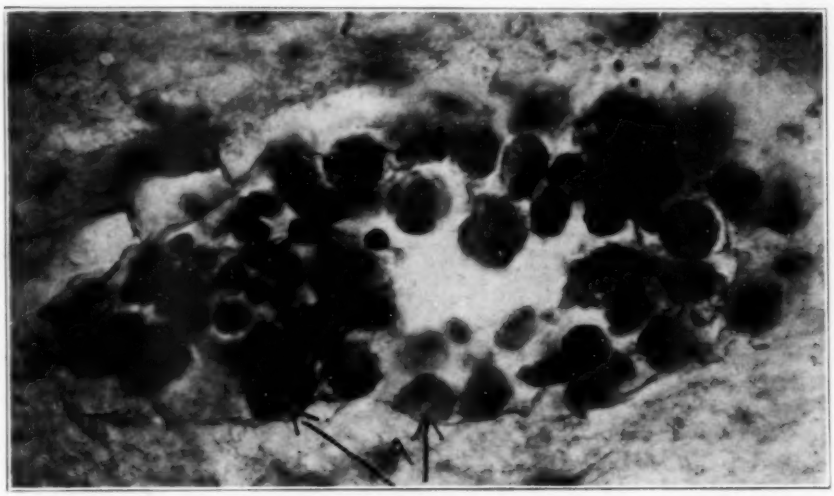

Fig. 9.—Photomicrograph (high power) showing the perivascular cell exudate with predominance of "large globoid cells." Granular corpuscles and lymphocytes can also be seen. *A* indicates large globoid cells. (Hematoxylin-eosin stain.)

difficulty. Reflex closure of the lids was performed well. There were no other apractic disturbances. Increasing apathy with incontinence of urine and feces was noted. Tenderness of the frontal and parietal regions of the skull with roentgenographic evidence of increased intracranial pressure also favored neoplasm. On the basis of the foregoing signs the diagnosis of a left frontal neoplasm was made, and this region was explored. At necropsy the pathologic process of encephalitis periaxialis diffusa was found to involve both frontal lobes and the corpus callosum.

The pupils were affected in different ways. No record was made in eleven instances; the pupils were normal in seven, reacted sluggishly in five, no reactions were obtained in three; a complete Argyll-Robertson syndrome and a partial Argyll-Robertson syndrome were each observed once; in four instances, they were unequal; in six, they were dilated.

There was no record of ocular movements in thirteen cases; in three they were normal. The most common finding was slight nystagmus (seven cases); a deviation or squint was noted in eight cases. In three instances unilateral external rectus paralysis was found. In one case bilateral external rectus palsy was mentioned. One record was made of paralysis of lateral gaze, one of upward gaze, one of unilateral ptosis and three of "diplopia and affected movements." Schilder's instance of apraxia of lid closure has already been mentioned.

Hearing.—Hearing was frequently affected toward the end of the illness and was in the nature of a psychic deafness.

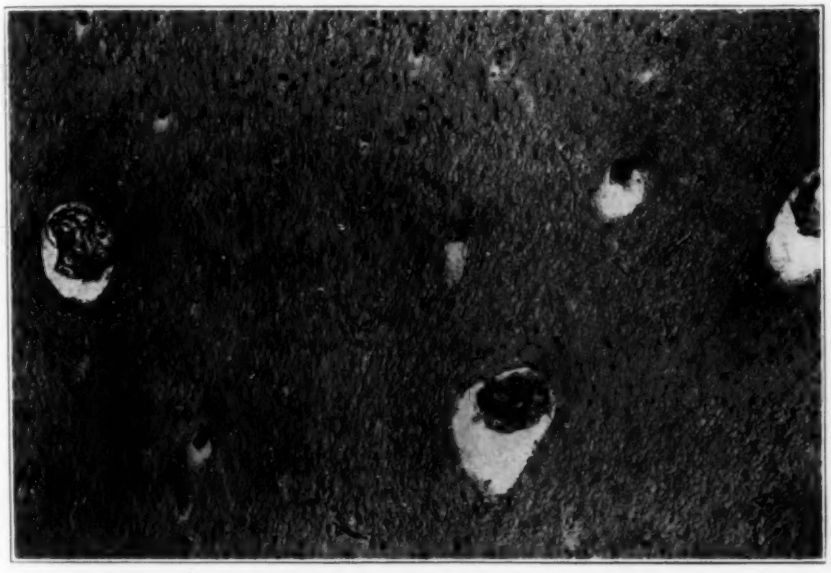

Fig. 10.—Photomicrograph of demyelinated region showing increased production of neuroglia and numerous blood vessels, with large empty spaces about them and a cellular exudate in the adventitial spaces of the vessel walls.

Disorders of Speech.—These disorders were prominent; no mention of them was made in seven cases; speech was normal in three cases. In the twenty-three remaining cases, various forms of aphasia and progressive loss of speech were described. In the later stages anarthria was frequently observed.

Motor System.—Involvement of the pyramidal system played an important rôle throughout the disease. Frequently, a monoplegia was one of the early noteworthy symptoms; diplegia, triplegia, hemiplegia or quadriplegia resulted, depending on the site and extent of the lesions.

No record of involvement was noted in six cases. Quadriplegia was noted in eleven instances; hemiplegia in five, diplegia in three, triplegia in two and a monoplegia in one. Naturally, contractures often followed; in six cases they were outstanding. The Babinski toe reflex and diminution or loss of abdominal reflexes were frequently found, and ran parallel with pyramidal tract disturbances.

As might be expected from a consideration of the extent of the pathologic condition, ataxia, dyssynergia and various types of tremors are frequently found. Occasionally a partial paralysis agitans syndrome is encountered.

Epileptic Seizures.—In eighteen cases epileptiform seizures were not mentioned. In ten cases they were generalized; in five they were of a localized jacksonian type.

Sensory Changes.—Sensory changes were observed in only eight cases; in six of these, diminution was noted, and in two hyperesthesia. The progressive mental deterioration precluded sensory testing in many cases. Were the patient alert and able to respond, sensory defects would undoubtedly be elicited more often.

Miscellaneous Symptoms.—Of particular interest is bronzing of the skin. It was found in the case of Siemerling and Creutzfeld, together with atrophy of the suprarenal glands. In the recent case described in *L'Encéphale,*[5] it was again mentioned. We have observed it in another patient (still living) in whom clinical evidence seems to indicate the presence of this disease.

Although the course of the disease was usually afebrile, in Stauffenberg's patient it was febrile throughout. Our case ran a definitely febrile course for one month; at the end there was an acute antemortem rise to 105.5 F.

Cerebrospinal Fluid.—In almost every case the cerebrospinal fluid was normal throughout the course. In one case, 16 cells were recorded; in another, a positive globulin content was observed. No fluid showed a positive Wassermann reaction; in one case, a positive reaction was obtained with the blood serum.

COMMENT

Our study of this case so far throws no light on the pathogenesis of the disease. It evidently began in the occipital lobes, although not at the extreme tip. The disease was bilateral and evidently spread forward by continuity. The peculiar "large globoid cells" observed in this disease resemble endothelial cells, and it is possible that they are associated with the proliferation of blood vessels that takes place in the affected regions.

THE SPONTANEOUS ESCAPE OF CEREBROSPINAL FLUID THROUGH THE NOSE

ITS OCCURRENCE WITH BRAIN TUMOR *

C. E. LOCKE, JR., M.D.
CLEVELAND

The patient who, without warning, suddenly develops a discharge of cerebrospinal fluid from the nose should at once be considered a "brain tumor suspect." [1] In cerebrospinal rhinorrhea the liquid is usually clear, does not stain the handkerchief, and flows more freely when the head is inclined forward. In the recumbent position, the tasteless fluid may run into the pharynx, the patient being unaware of its presence. The amount of fluid discharged in twenty-four hours varies from 50 to more than 1,000 c.c., and by the usual tests it shows no variations from the fluid obtained by spinal puncture. The discharge may be either continuous or intermittent. When intermittent, the onset of the rhinorrhea may be accompanied by relief from signs and symptoms of intracranial pressure.

The patient who, without warning, suddenly develops a discharge of opinion among previous authors concerning the underlying cause of spontaneous cerebrospinal rhinorrhea and concerning the location of the communication between the intracranial spaces and the nose.

HISTORICAL NOTES

Charles Miller [2] was the first to show definitely that cerebrospinal fluid might escape spontaneously through the nose. The following quotation from his brilliant communication read before the Edinburgh Medico-Chirurgical Society in 1826 illustrates his careful description. "The opening through which the water had distilled into the nostrils was a foramen—above and to the right of the crista galli; it might have admitted four bristles and had a direct communication with the nasal cavity."

More than a century prior to Miller's article and even before the recognition of the normal existence of the cerebrospinal fluid, Thomas

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* From the Department of Neurological Surgery, Cleveland Clinic.

* Read before the American Neurological Association, Washington, D. C., May 6 and 7, 1925.

1. All patients with symptoms and signs that suggest brain tumor, who enter Dr. Cushing's neurologic service at the Peter Bent Brigham Hospital, are temporarily placed in the "brain tumor suspect" group. They remain classified as such until this diagnosis has been either proved or disproved. At the Cleveland Clinic a similar method of classification has been instituted.

2. Miller, Charles: Case of Hydrocephalus Chronicus, with Some Unusual Symptoms and Appearances on Dissection, Tr. M. Chir. Soc. Edinburgh **2**:243, 1826.

Important Findings in Fourteen Cases of Spontaneous Cerebrospinal Rhinorrhea Found in Literature

Author and Reference	Age; Sex*	History	Examination	Rhinorrhea	Ventricles Dilated	Postmortem		
						Communication	Cerebral Tumor	Meningitis
Miller [2]..... 1826	♂ 16	Enlargement of head commenced at 11 months and continued to 14 years, at which time rhinorrhea appeared; death at 16 preceded by stupor	At 14 circumference of head 31 inches; normal mentality	About 30 to 60 c.c. daily	Yes	An opening through the floor of the anterior fossa was located above and to the right of the crista galli and connected directly with the nose	No	Purulent meningitis
Paget [9]..... 1879	♀ 49	Not reported; onset of rhinorrhea 18 months before; cessation and signs of meningitis before death	Not reported	Amount ?	Incomplete report	Incomplete report	Incomplete report (polyps in antrum)	Purulent meningitis under frontal lobe and at base of brain
Baxter [10].... 1892	♀ 35	Bitemporal headaches; diminished vision; death preceded by general convulsions and coma	Bitemporal optic neuritis; bitemporal hemianopia; marked loss of vision	Amount ?	Incomplete report	Incomplete report ...	(The examination and history are suggestive of pituitary tumor; perhaps Baxter overlooked it at necropsy)	Incomplete report
Leber [1] 1883	♀ 22	Enlarged head from birth; always a weak child and undersized; headaches, dizziness, convulsions, and partial loss of vision; onset of rhinorrhea at 20	Examination at 15 showed large head and reduced vision of right eye and left eye	From left nostril, flow of from 5 to 22 c.c. an hour	Dilatation of lateral third and fourth ventricles	A round funnel shaped excavation in the region of the sella turcica was found; at the bottom of this depression were tiny perforations	No	Turbid cerebrospinal fluid
Nothnagel [19] 1883	♂ 20	Head trauma at 16 with nausea, vomiting and fever; later enlargement of head, staggering gait, convulsions of varying intensity; onset of intermittent rhinorrhea at 20; symptoms always improved with discharge of fluid from the nose; finally stopped for 13 days, coma, fever and death	At 17 partial loss of vision, optic neuritis, wide base gait and Romberg sign positive; later more loss of vision; nystagmus, anosmia and spasticity of lower extremity	Intermittent, from 60 to 70 c.c. daily; then stopped 13 days before death	Yes	Cribriform plate transparent and overlying dura like tissue paper	Tumor of corpora quadrigemina	?
Gutsche [11]... 1895	♂ 35	Perfect health; onset of rhinorrhea at 35; 58 days later patient died with symptoms of meningitis	After onset of rhinorrhea pus found in nasal sinuses; later signs of meningitis	250 c.c. daily; left nostril	Yes	A probe may be passed from above through the ethmoid directly into the nasal cavity	Tumor of hypophysis	Yes
Mermod [12]... 1896	♂ 36	Severe right frontal headaches; several operations on infected nasal sinuses followed by rhinorrhea onset at 36, then signs of meningitis; trepanation; death	Meningeal signs shortly before death	Intermittent flow with relief of headache; amount ?	Yes	An opening beside crista galli and another near foramen cecum	No	Yes
Güntz [20]. ... 1897	♂ 20	Headaches, dizziness; onset of rhinorrhea at 20; then symptoms of meningitis followed by death	Choked disks; increase in size of head; signs of meningitis before death	Right nostril; amount ?	Yes	Caries of ethmoid bone with opening into nasal cavity	No	Yes

Guntz [20]... 1897	♂ 20	Headaches, dizziness, onset of rhinorrhea at 20; then symptoms of meningitis followed by death	Choked disks; increase in size of head; signs of meningitis before death	... amount ?		... bone with opening into nasal cavity		
Wollenberg [21] 1898	♂ 22	At 19 diminished vision in the right eye was noted; headaches and vomiting; onset of rhinorrhea at 22; finally stupor; high temperature and dyspnea; cessation of rhinorrhea and death	At 19 choked disks; later left facial palsy; ringing of ears; inclination of head to left; divergent strabismus; bilateral exophthalmos; anosmia and general convulsions	Both nostrils; 150 c.c. in 12 hours; intermittent; flow stopped before death	Yes	Several openings from base of anterior fossa into ethmoid and frontal sinuses; large opening to right of crista galli connected with the anterior horn of the right lateral ventricles	Two tumors of right occipital lobe	Yes
Meyer [22]..... 1905	♂ 20	Head injury at 14 and a year following headache developed; blurring of vision and neuralgia of left side of face; symptoms grew worse; rhinorrhea began at 20; when it stopped patient became stuporous and had general convulsions, at 20 died in status epilepticus	.....	Intermittent; amount ?	Yes	Funnel shaped opening from nose into anterior horn of right lateral ventricle	Adenoma of pineal	?
Vigouroux [23] 1908	♂ 28	Rhinorrhea for some years and loss of smell	Some loss of power of left side of body and left sided exophthalmos and anosmia	Intermittent, 800 c.c. in 24 hours	Yes	In base of anterior fossa two funnel shaped depressions lined with dura and tiny perforations in their floors communicating with the nasal cavity	Papillomatous tumor of choroid plexus of fourth ventricle	Yes
Souques and Odier [24] 1917	?	Headaches and vomiting present for 9 years and occasional epileptic attacks; rhinorrea; later patient became comatose and died in 4 days	Roentgen ray showed enlargement of pituitary	From 200 to 500 c.c. in 24 hours; from right nostril; continued without stopping until death	Yes	Well formed fistula between anterior horn of lateral ventricle and nasal cavity through cribriform plate	Tumor of right cerebellopontile angle	Yes
Cushing [15]... 1921	♂ 41	Deafness right ear for 17 years; 3 years before examination, onset of occipital headaches; numerous operations on nasal sinuses followed by watery discharge from nose; cerebellar exploration by Dr. Cushing disclosed a right acoustic neuroma; partial intracapsular enucleation; satisfactory recovery and return to work; influenza 2 weeks before examination; cold; during paroxysm of coughing an abundant discharge of clear watery fluid from nose; dripping persisted; signs of meningitis; death	Nerve deafness of right ear; lateral nystagmus; unsteady gait; Romberg sign positive; bilateral choked disks; slight exophthalmos; anosmia; roentgen-ray evidence of increased intracranial pressure and sella changes; slight weakness of right face; paresthesias of left face; pulsating protrusion into nose through sphenoid and ethmoid region at site of nasal operation	Intermittent; amount ?	Yes	Opening through left ethmoid region contained a protrusion of frontal lobe covered with dura; anterior horn of left lateral ventricle communicated directly with the nasal cavity	Right acoustic tumor with multilocular arachnoid covered cyst	Yes
Locke,..... Case 1	♀ 46	Ten years before headaches; deafness and tinnitus in right ear; 3 years before examination onset of cerebellar symptoms and rhinorrhea (Case 1)	Cranial nerve signs; early choked disk, cerebellar signs (Case 1)	Right side, 10 c.c. in 10 minutes	Slightly dilated	Opening through right side of cribriform plate into nose	Tumor of right cerebellopontile angle and of frontal lobe	Yes

* In this column, ♂ indicates male; ♀, female.

Willis [3] described a case in which clear fluid was discharged from the nose. Some years later, in 1762, Morgagni [4] reported a similar case. It is possible that both of these were cases of cerebrospinal rhinorrhea.

In 1834, King [5] presented a case to the Westminster Medical Society in which the condition, although not recognized, was undoubtedly cerebrospinal rhinorrhea. In the discussion which followed his paper, it was decided that no attempt should be made to stop the flow of the fluid from the nose, as it probably was a "protective mechanism of animal economy, to ward off an already evident general anasarca."

In 1877, Tillaux [6] reported a case in which a watery discharge from the nose was proved by laboratory test to be cerebrospinal fluid. Most of the more recent authors have given Tillaux the credit for the first description of cerebrospinal rhinorrhea, but his work appeared many years after Miller's brilliant paper.

In 1883, Leber [7] reported a case of cerebrospinal rhinorrhea and suggested that its cause was internal hydrocephalus.

A noteworthy monograph on this subject was compiled by St. Clair Thomson,[8] in 1899. He reported one case of his own and collected from the literature eight undoubted and twelve probable cases of cerebrospinal rhinorrhea. Thomson came to the conclusion that cerebrospinal rhinorrhea was a complication of Quincke's serous meningitis, his opinion being based on the four necropsy reports that he was able to find (Paget,[9] Baxter,[10] Gutsche [11] and Mermod,[12] as shown in the table).

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3. Willis, Thomas: Opera Omnia; Cerebri Anatome, Nervorumque descriptio et usus; quibus accessit viri cuiusdam clarissimi de ratione motus musculorum tractotus singularis, Geneva, 1676.

4. Morgagni, J. P.: De sedibus et causis morborum per anatomen indagatis libri quinque, Venice, 1762 (liber 1, ep. xv, art. 21).

5. King: Case Report of Clear Fluid Discharge from Nose, London M. & S. J. **4**:823, 1834.

6. Tillaux, P. J.: Traité d'anatomie topographique avec applications à la chirurgie, Paris, 1877, p. 56.

7. Leber, T.: Ein Fall von Hydrocephalus mit neuritischer Sehnervenatrophie und continuirlichen Abträufeln wässeriger Flüssigkeit aus der Nase, Arch. f. Ophth. **29**:273-292, 1883.

8. Thomson, St. Clair: The Cerebrospinal Fluid, Its Spontaneous Escape from the Nose, London, 1899.

9. Paget, Sir James: A Case of Polypi of the Antrum in Which Watery Fluid Dropped from the Nostril, Tr. Clin. Soc. London **12**:43-47, 1879.

10. Baxter, E. B.: A Case of Paroxysmal Clonic Spasms of the Left Rectus Abdominis with Symptoms Pointing to the Existence of a Gross Intracranial Disease, Brain **4**:525-530, 1881-1882.

11. Gutsche, Phillip: Zur Pathogenese der Hypophysistumoren und über den nasalen Abfluss, sowie das Verhalten des Liquor cerebrospinalis bei einer Struma pituitarea, Centralbl. f. Laryngol. **11**:460, 1895.

12. Mermod: Méningo-encéphalite consécutive à l'exploration d'un soi-disant sinus frontal, Ann. de Mal. de l'Orielle et du Larynx **22**:337-344, 1896.

Schwab and Green [13] summarized the reported cases up to 1905 and added one of their own. In common with previous writers, they pointed out the fact that optic neuritis is usually associated with cerebrospinal rhinorrhea. They concluded that they were dealing with an independent pathologic entity, an intracranial inflammation which not only involved the optic nerve but also eroded the base of the cranium, permitting an escape of cerebrospinal fluid.

Even though it was written seventeen years ago, there has been no subsequent work which compares with Dr. Cushing's section on Surgery of the Head in Keen's Surgery.[14] In this chapter he discusses cerebrospinal rhinorrhea and shows the close relation between the ethmoid mucous membrane and the floor of the anterior cranial fossa. At a later date Dr. Cushing [15] also reported a case of spontaneous cerebrospinal rhinorrhea with the pathologic demonstration of the fistula (Case 13 in the table).

An article written in 1923 by Loftus [16] suggests that the leakage occurs through the remains of the embryonic craniopharyngeal ducts. Loftus mentions reports of only four postmortem examinations, two of which were the incomplete reports of Paget and Baxter.

CLINICAL COURSE AS ILLUSTRATED BY CASE REPORTS

During my all too short service as "assistant étranger" in Prof. Pierre Marie's clinic at the Salpêtrière, Paris, I had the opportunity of studying the following case which Professor Marie suggested that I report. More recently Professor Roussy very kindly forwarded to me the results of the postmortem examination.

CASE 1.—*Signs and symptoms of cerebellopontile tumor; discharge of clear fluid from nose; meningitis; death; postmortem revealed tumor and communication between nose and anterior cranial fossa*

A woman, aged 46, who entered the Salpêtrière in June, 1922, gave unimportant familial and personal histories except for the existing illness which had commenced ten years before with generalized headaches and ringing in the right ear, followed by complete deafness on that side. Shortly afterward the patient had first noticed paresthesia of the right side of the face which gradually progressed until there was almost entire loss of feeling. About three years before examination, she had first noticed loss of the sense of smell. Cerebellar signs did not develop until a year before admittance, when the patient found that she staggered from side to side and a neighbor accused her of being intoxicated. About the same time she noticed that her hands were very unsteady. The

13. Schwab, S. J., and Green, J.: A Case of Cerebrospinal Rhinorrhea with Retinal Changes, Am. J. M. Sc. **129**:774-781, 1905.

14. Cushing, Harvey: Keen's Surgery **3**:124-126, 1908.

15. Cushing, Harvey: Acoustic Neuromas, Laryngoscope **31**:209 (April) 1921.

16. Loftus, J. E.: Cerebrospinal Rhinorrhea with Report of a Case Laryngoscope **33**:617-632 (Aug.) 1923.

headaches at that time were severe. Difficulty in pronounciation and difficulty in swallowing fluids were also experienced then for the first time. Quite suddenly about one year before entering the hospital, without any injury, the patient developed a copious discharge of warm clear fluid from the nose, with a coincident lessening in the severity of the headache. From that time the discharge of fluid from the nose had continued, coming more freely when the head was flexed on the chest. When lying down the patient could feel the fluid run down into her pharynx. The sight of her right eye had been partially lost in youth as the result of an injury, but the vision of the left eye had not been impaired during this illness.

Examination.—The patient was well developed, but poorly nourished, middle-aged and French. No finding of any consequence was elicited in the general physical examination.

The findings in the neurologic examination were as follows:

Head: Normal in size and shape, but always held slightly tilted toward the right. Slight dilatation of the veins of the upper eyelids. Percussion note of the head normal. No exostoses nor tender points on the skull. With the patient in a sitting position and the chin flexed on the chest there was an initial copious discharge from the nose of a clear, watery fluid, this being followed by a less profuse flow amounting to about 5 c.c. in ten minutes.

Neck: No rigidity nor tenderness.

First Cranial Nerve: Bilateral loss of olfactory sense, subjective and objective.

Second Cranial Nerve: Right eye: She can distinguish only large objects: vision is insufficient for visual field examination; an old corneal cicatrix is present. Left eye: visual acuity normal, visual field normal; fundus showed some dilatation of the retinal veins and slight haziness of the nasal and inferior borders of the disk, but no actual elevation; the disk was a little pale on the temporal margin.

Third, Fourth and Sixth Cranial Nerves: Subjective: diplopia. Objective: slight exophthalmos, more marked on the right side and also some ptosis on the right. Right eye divergent. Pupils contracted to 3 mm. and equal; on the left prompt reaction to light and in accommodation, but only consensual reaction of the right eye. Nystagmus present.

Fifth Cranial Nerve: Subjective: crawling sensation, followed by loss of sensation of right side of face. Objective: Motor: paresis and atrophy of right masseter and temporal muscles, and deviation of the jaw to the right. Sensory: marked hypesthesia over all three divisions of the right trigeminal nerve. Reflex: loss of corneal and nasal reflex on right.

Seventh Cranial Nerve: Subjective: negative. Objective: Motor: no pronounced asymmetry of forced movements of facial muscles, but the facial expression of both the upper and lower facial musculature of the right side was less active than on the left. Sensory: taste on the anterior two thirds of the right side of the tongue was diminished.

Eighth Cranial Nerve: Acoustic division: Subjective: ringing in the ears followed by deafness. Objective: loss of both air and bone conduction of the right ear. Bone conduction was lateralized to the left. Acuity of left ear good. Vestibular division: Subjective: dizziness and difficulty in maintaining balance. Objective: nystagmus present and inability to balance on either foot.

Ninth and Tenth Cranial Nerves: Subjective: trouble in speaking, and choking when swallowing. Objective: Motor: asymmetry of palate, less active on the right; marked dysarthria of typical slurring type; dysphagia. Sensory:

taste on posterior one third of the tongue impaired on the right side. Reflex: bilateral loss of pharyngeal reflex.

Eleventh Cranial Nerve: Trapezius and sternomastoid muscles worked equally and well.

Twelfth Cranial Nerve: No deviation nor atrophy nor fibrillations of tongue.

Lobes of the Brain: Frontal: memory good, no loss of orientation nor change in character, but bilateral olfactory loss. Precentral: no convulsion; no paresis; no paralysis; muscular action good and equal on both right and left; no spasticities nor contractures. Postcentral: no subjective nor objective sensory signs of a cortical nature. Other sensory findings described under the fifth nerve and below. Temporal: no uncinate gyrus attacks nor dreamy states, and no aphasia nor temporal lobe hemianopia. Postparietal: no astereognosis nor loss of muscle sense, no apraxia and no alexia. Occipital: no visual hallucinations and no hemianopia. Cerebellar: Position of the head and trunk was that of slight inclination to the right. The Romberg sign was positive and the patient fell to both the right and the left, as well as backwards. Walking was possible only with assistance, and the gait was extremely ataxic. Pulsion tests showed poor balance, especially to the right. Lateral nystagmus was prominent and was about equal, whether the patient looked to the right or left. The finger to nose and finger to thumb tests were poorly executed, perhaps more poorly on the right side and with considerable hypermetria on both sides; the heel to knee test showed a great deal of hypermetria on both sides; adiadokokinesis, static ataxia and past pointing were marked right and left; dysphagia and dysarthria were very evident. Hypotonia was more marked on the left side.

Extremities (Upper and Lower): No paralysis, no atrophies nor hypertrophies; no rigidity nor contractures. Some hypotonia especially on the left. No impairment of perception of touch except over the right fifth nerve. Diminished temperature sensation of the left arm, front and back, of the left upper chest and also of the entire left side of the head.

Reflexes: Patellars equal and hyperactive; Achilles equal and slightly hyperactive; radial exaggerated on the right and diminished on the left; abdominals equal and active; Oppenheim present, bilateral; atypical Babinski right and left; no sphincter loss.

A roentgenogram of the skull showed considerable enlargement of the sella turcica.

Laboratory Tests: Blood, Bordet-Wassermann reaction negative. Urine, normal. Fluid draining from the nose: (1) absolutely water clear with no sediment nor opalescence; (2) albumin 0.05 gm. per 100 c.c.; (3) Fehling's reduction normal; (4) cell count, sixteen lymphocytes; (5) Bordet-Wassermann, negative.

Clinical Diagnosis: Intracranial tumor of the right eighth nerve with cerebrospinal rhinorrhea.

The signs and symptoms in this patient were characteristic of a cerebellopontile tumor except that vision was conserved, and there was only slight edema of the optic disks. Without doubt the drainage of cerebrospinal fluid acted as an effective decompression and prevented high-grade intracranial pressure.

Since the lesion seemed far advanced and the general condition of the patient was rather poor, Prof. Pierre Marie did not advise operation. Extensive roentgen-ray treatment was used without avail, and the patient died some twelve months later.

Postmortem Examination.—By the courtesy of Professor Roussy, I am able to include the following report of the postmortem examination. There was present a voluminous tumor of the right cerebellopontile region. This tumor was of the size of an Indian chestnut and had destroyed all of the posterior part of the pons, and had also invaded the left side. It had penetrated the right cerebellar hemisphere and had extended to and into the vermis. In addition, another tumor, the size of an almond, was present in the extreme anterior

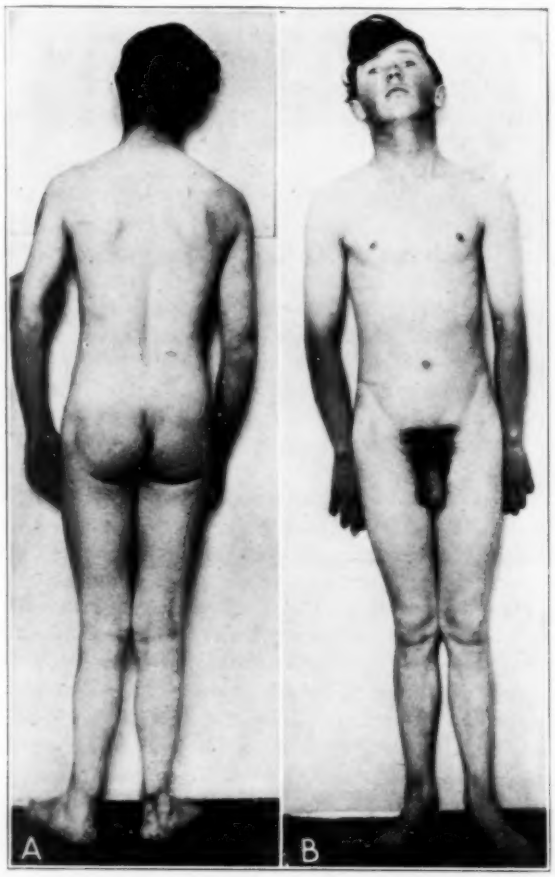

Fig. 1 (Case 3).—Patient with cerebrospinal rhinorrhea. The inclination of the head and trunk to the right, the slight enlargement of the head, the feminine distribution of pubic hair and the absence of body hair may be noted.

portion of the left frontal lobe. The lateral ventricles were but slightly dilated, and there was a slight dilatation of the third ventricle. In the region of the cribriform plate of the ethmoid, on the right side, there was an opening which communicated with the nasal cavity. In this region and at the base of the brain there was a purulent meningitis. The histologic examination of both tumors showed a "gliome périphérique."

Case 2.—Because of its marked similarity to the preceding case, mention should be made of the case of a patient who came under my care in 1920,

during my service as Dr. Cushing's assistant at the Peter Bent Brigham Hospital. A complete record of this case has been published by Dr. Cushing in a report on acoustic neuroma (Case 14 in the table).

A man, aged 41, had had symptoms of a right acoustic tumor for seventeen years. He had had various intranasal operations which had caused an ethmoidal herniation of the dura. Several months after a successful intracapsular enucleation of the tumor the patient developed a cerebrospinal rhinorrhea at the site of this dural herniation, with resultant meningitis and death. Necropsy showed a communication between the anterior horn of the left lateral ventricle and the nasal cavity at the site of the ethmoidal opening.

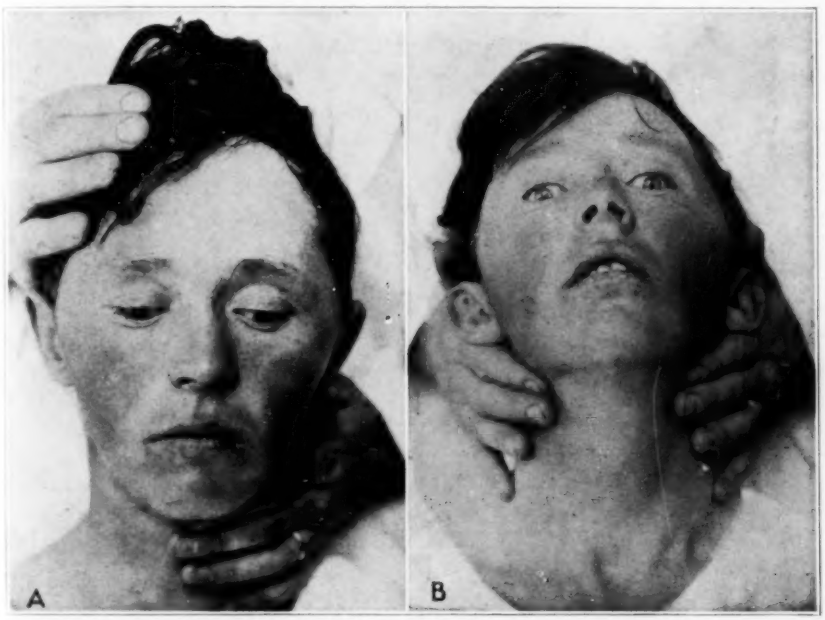

Fig. 2 (Case 3).—Patient with cerebrospinal rhinorrhea. *A*, with the head in its normal position, the inability of the eyes to look upward and attenuation of the lateral half of the eyebrows and the scanty beard may be noted; *B*, only with the head in dorsal flexion is it possible for the eyes to be directed in a horizontal plane.

Case 3.—*A young man with a very large head; history of clear fluid from the nose two years before; sudden onset of stupor disappearing after operative puncture of ventricle; stupor; coma; spontaneous rhinorrhea; return to consciousness.*

A man, aged 21, entered the neurosurgical service of the University of California Hospital, Feb. 10, 1924, in a stuporous condition. The familial history was negative except that one grandfather died of tuberculosis. Even when he was a small child he had a large head, and his last hat was size 7¾. He had had dull frontal headache for about one year. He had always been of a retiring and solitary disposition and was backward in school. Two years before, he had fallen from a haystack and lost consciousness for five minutes, but there had been no other sequelae to this accident except for a discharge of clear watery fluid from the

nose. This came mostly from the right nostril, especially when the head was bent forward. It had continued intermittently until about two months before he entered the hospital when it ceased during an illness diagnosed as influenza. On his recovery from this illness it had been noticed that the boy's memory, especially of recent events, was poorer than usual, and there was one severe attack of dizziness. The patient grew progressively worse, and for the seven days preceding examination he had been in a sleepy dazed condition, from which he could be but partially aroused to obey commands.

Examination showed the patient to be a rather well developed and well nourished youth of apparently 16 or 17 (Fig. 1), in a drowsy state and yawning frequently. The temperature was 36.5 C., the pulse rate 60; respiration 16; blood pressure, systolic 102, and diastolic 62. The abnormal findings in the general physical examination were: a general enlargement of the head, a high palatal arch with crowded teeth, rough dry skin, scanty beard, feminine distribution of the pubic hair, lateral half of eyebrows thin and absence of hair on the body. The urine examination showed specific gravity 1.032, a trace of albumin, no sugar and from 1 to 3 white blood cells per high dry field. The blood count was normal; the Bordet-Wassermann reaction was negative.

The examination of the cranial nerves showed diminished olfactory acuity of the right nostril. There was a history of poor vision, and, in the ophthalmologic examination both eyes showed blurring of the disk outline with perivascular streaking, obliterated cup and distinct pallor of the disks. The pupils were equal and the reflexes normal. There was no nystagmus nor exophthalmos, but a bilateral paralysis of upward eye movements was present (Fig. 2). The motor, sensory and reflex tests of the trigeminal were negative. A slight weakness of the left lower facial movements was noted, perhaps habit. There was no loss of auditory acuity and no sign of vestibular involvement; no dysarthria nor dysphagia, nor regurgitation of fluids through nose. The action of the sternomastoid and trapezius muscles on the two sides was equal, and the tongue protruded in the midline without tremor or atrophy.

The motor and sensory examination gave normal findings throughout. There were no atrophies nor hypertrophies, and no tremors. Considerable rigidity of the neck was present. Kernig's sign was bilaterally present. The deep reflexes, biceps, triceps, radials, patella and Achilles, were active and equal; and so were the superficial reflexes, corneal, upper and lower abdominal, cremaster and plantar. No pathologic reflexes were present. There was incontinence of urine but no involuntary bowel movements. An inventory of the localizing signs and symptoms of the various lobes of the brain gave no significant findings, loss of memory and lack of orientation of time and place being considered as due to the stupor and not as of localizing significance. The preoperative diagnosis was chronic internal hydrocephalus probably due to a slow growing pineal tumor.

Operation.—On Feb. 14, 1924, under local anesthesia, I made a bilateral ventricle puncture and air injection. The roentgen-ray studies revealed marked symmetrical enlargement of the lateral ventricles and enlargement of the third ventricle (Figs. 3 and 4). Following this procedure the stupor disappeared and the patient became bright and talkative. The pulse rate increased from 60 to 88. However, on the morning of February 16, he relapsed into a stupor. February 25, Dr. Naffziger made a right occipital osteoplastic flap under ether anesthesia, revealing a marked pachymeningitis interna extending toward the midline and to a less marked degree toward the mastoid, thus preventing any attempt to explore the pineal region. The immediate operative convalescence

was satisfactory, but then a series of infections developed—mastoiditis, erysipelas of the face and neck and multiple abscesses over the head and extremities. During all this time the patient was in either deep stupor or coma. April 28, after over two months, the patient very unexpectedly became bright and talkative. A cerebrospinal rhinorrhea was at once suspected and was easily verified by holding the patient's head over the edge of the bed. The fluid was clear and dropped at the rate of 30 drops a minute, 20 c.c. of fluid being collected in ten minutes. The cell count of the fluid was 8, all small mononuclears; the globulin negative. Benedict's solution was faintly reduced. May 5, the rhinorrhea had ceased; the patient was again drowsy. The pulse rate had dropped

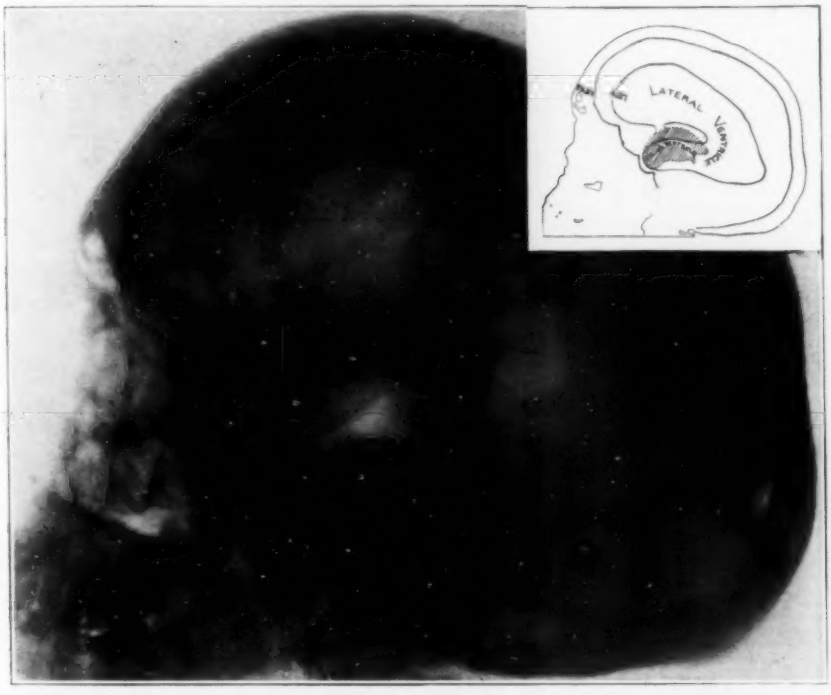

Fig. 3 (Case 3).—Lateral ventriculogram of cerebrospinal rhinorrhea. The marked dilatation of the lateral ventricle and the enlargement of the third ventricle may be noted; insert shows the outline of the third ventricle which may be readily distinguished from the lateral ventricles.

from 70 to 53 and respirations from 16 to 12. A response to a follow-up letter dated May 13, 1925, states that the patient lay helpless in bed and was untidy and disoriented until a few months before. He is now on his feet and is becoming alert. He has little memory of the year following the operation. No recurrence of rhinorrhea has been noted.

PATHOLOGY

Rather elaborate theories have been advanced concerning the cause of cerebrospinal rhinorrhea, but up to the present no effort has been made to study the published reports of necropsies in these cases. Since,

undoubtedly, much information may be gained by such a study, I have searched the literature and found reports of fourteen fatal cases of spontaneous cerebrospinal rhinorrhea in which necropsy was performed. The important findings in these cases are shown in the table.

Among these reports, those of Paget and Baxter are so incomplete as to be of no value. In each of the remaining twelve reports internal hydrocephalus was found. In eight cases the internal hydrocephalus was

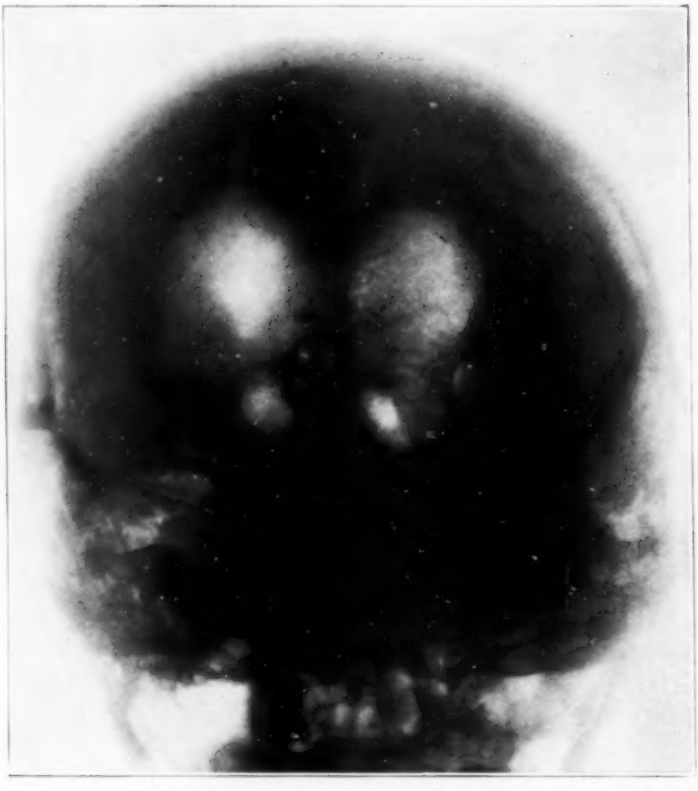

Fig. 4 (Case 3).—Anterior posterior ventriculogram of cerebrospinal rhinorrhea showing the marked dilatation of the lateral ventricles.

due to a cerebral tumor which caused an obstruction within the ventricle system. Two were cases of congenital hydrocephalus in which rhinorrhea developed in early adult life after the fontanels and sutures had closed, and two were cases of hydrocephalus of the adult type.

Eleven of the twelve reports included a description of unmistakable openings connecting the floor of the anterior cranial fossa with the nasal cavity. In the twelfth case only a thinning and no opening was found, but the history in this case definitely described a cessation of rhinorrhea thirteen days before the death of the patient. It seems

probable that in this case the basal meningitis found at necropsy may have closed the opening through which the cerebrospinal fluid passed into the nose, thus preventing its detection. The location of the meningitis under the frontal poles also suggested that it had an ascending origin from the nose through a perforation in the floor of the anterior cranial fossa.

In seven of the cases there were communications through the cranial base, between the cisterna basalis and the nose. In three there was a direct communication through the bony cranial floor, between the anterior horn of a lateral ventricle and the nasal cavity. In one case it seemed

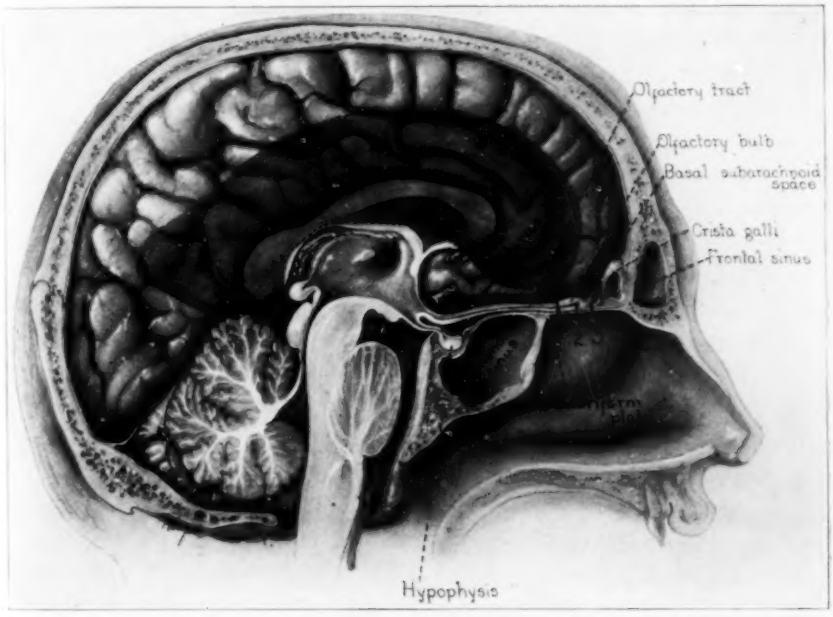

Fig. 5.—The three routes by which the cerebrospinal fluid reached the nose in this series of cases: (1) an opening from the floor of the anterior horn of a widely dilated lateral ventricle through the cribriform region into the nose; (2) an opening from a persistent lumen in the olfactory bulb through the cribriform plate into the nose; (3) an opening from the basal subarachnoid cistern through the cribriform plate into the nose.

possible that the olfactory bulb had maintained its embryonic ventricular lumen from which a fistula into the nose had formed.

Figure 5 illustrates these three routes by which, as proved by necropsy, cerebrospinal fluid may reach the nose. The presence of purulent basal meningitis was recorded in ten of the twelve reports of necropsies. Since in the other two cases the clinical course suggested a terminal meningitis, it would appear that meningitis is usually the immediate cause of death, if we may judge from this small series of cases.

COMMENT

Obstruction of the circulation of the cerebrospinal fluid and increased intracranial pressure are no doubt the two necessary factors in the formation of a fistula between the anterior cranial fossa and the nose. Brain tumor is the most common lesion in which there is an association of these two causative factors.

In the presence of only the former factor, spontaneous cerebrospinal rhinorrhea does not often occur, for we do not find it in association with the hydrocephalus of infancy in which the open fontanels and sutures allow decompression. It is possible that increased intracranial pressure causes atrophy of the cribriform plate. This pathologic condition, perhaps, is identical in nature with convolutional atrophy of the cranial vault, which is so often associated with brain tumors in children or in young adults. The dura overlying the cribriform region is especially susceptible to penetration because of the tiny holes which are normally present for the exit of the olfactory nerves, and, furthermore, the arachnoid membrane and the subarachnoid space continue for a short distance along these nerves. In their celebrated work, Key and Retzius [17] found that when blue gelatine injection masses were introduced into the subarachnoid and subdural spaces they sometimes reached the capillaries of the nasal mucous membrane. Also, in a recent investigation in which I [18] have been engaged, it was found that when celloidin masses were injected under pressure into the subarachnoid spaces of the dog, they frequently leaked from the nose. Later, when the celloidin mass had hardened and the skull and brain had been corroded away, fine filaments from the cast of the subarachnoid spaces appeared to extend into the upper nasal regions. This leakage through the nose, however, did not occur in injections in the human cadaver.

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18. Locke, C. E., and Naffziger, H. C.: Cerebral Subarachnoid System, Arch. Neurol. & Psychiat. **12**:411-418 (Oct.) 1924.

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23. Vigouroux, A.: Ecoulement de liquide céphalorachidien; Papillome des plexus choroides du iv^e^ ventricule, Rev. neurol. **14**:281-285, 1908.

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When the thin cribriform plate is atrophied, and the normal openings in the overlying dura and arachnoid are enlarged by increased intracranial pressure, there remains only the ethmoid mucous membrane between the cerebrospinal fluid spaces and the nasal cavity; and this membrane evidently is unable to withstand the strain thus placed on it.

Our present physiologic conception is that the principal source of the cerebrospinal fluid is the choroid plexus. Why then should there be a continuous and profuse flow of cerebrospinal fluid in cases in which there is an intraventricular obstruction and a proved communication between the cisterna basalis and the nose? It is true that the cisterna basalis has a large capacity, but how is its fluid replenished when the source of supply has been cut off? Further investigation will be necessary to clear these points. It may be that we still have not the correct conception concerning the circulation of the cerebrospinal fluid, and that more fluid than we suspect is formed in the subarachnoid spaces. Several other explanations, however, present themselves. Perhaps the obstruction in the ventricle system is incomplete. The extraventricular portion of the choroid plexus may be excessively active. In hydrocephalus there may be accessory openings between the cerebral ventricles and the subarachnoid spaces.

The intermittent nature of many of the cases of cerebrospinal rhinorrhea may be accounted for by a localized, ascending inflammation, the exudate from which may close the fistula for a time until the accumulation of the fluid has caused sufficient pressure for it to break through again.

TREATMENT

The only rational form of treatment for this condition is one directed toward the relief of the obstruction of the cerebrospinal fluid pathways. Should there be localized signs of an accessible intracranial tumor, its removal should be attempted. However, too great an operative risk should not be taken, as some patients with rhinorrhea and brain tumor have lived for many years, the cerebrospinal leak acting as an effective decompression. The following question is immediately suggested: Could hydrocephalus be treated successfully by establishing surgically an artificial communication into the nose? Such a procedure would be justified only in a moribund patient. For, although some spontaneous leaks of the cerebrospinal fluid through the nose may persist for years, operative openings through the nose into the cerebrospinal spaces nearly always result in meningitis and death. In the belief that choked disks may be due to infection of the nasal sinuses, rhinologists frequently puncture the ethmoid and sphenoid sinuses of patients with cerebral tumor. Because of the attenuation of the base of the cranium in these

cases, the puncturing trocars not infrequently reach the intracranial spaces, and a leakage of the cerebrospinal fluid results, with a certain fatality.

CONCLUSIONS

1. In every one of the series of proved cases studied, spontaneous cerebrospinal rhinorrhea was associated with internal hydrocephalus and increased intracranial pressure. The most common lesion which produces a combination of these two factors is a cerebral neoplasm, but inflammatory or congenital obstruction of the cerebrospinal fluid also may be responsible.

2. In this series the communication between the nose and the cerebrospinal fluid pathways occurred through the cribriform plate.

BULBOCAPNIN

ITS USE IN THE TREATMENT OF TREMOR AND IN THE EXPERIMENTAL PRODUCTION OF BASAL GANGLION SYMPTOMATOLOGY *

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De Jong [1] of Amsterdam demonstrated that the tremor of paralysis agitans may be controlled by the use of bulbocapnin, and by administering larger doses of this drug to cats he produced a syndrome simulating catatonia. He first reported this work from the Binnen-Gasthuis of Amsterdam. His original problem was the experimental production of catatonia, and followed the work of Frölich and Meyer on "Katalepsie." [2]

Bulbocapnin is one of eleven alkaloids from *Corydalis cava*. The nineteenth edition of the United States Dispensatory gives four alkaloids in this plant, one of which is bulbocapnin, but Gademar of Marburg has isolated eleven. He has developed a process by which the pure alkaloid may be isolated from the plant. The bulbocapnin of the United States Dispensatory, being combined with other alkaloids, is extremely toxic, and should not be used in the doses herein mentioned. De Jong obtains his bulbocapnin from Gademar, and has recently been working on this problem with Schaltenbrand of Hamburg. Chemically, bulbocapnin is similar to apomorphin.

Corydalis cava was used, according to Peters, as early as 1526. In that year the Herb Book of Andreae Matthioli was published, in which a description of *Corydalis cava* was given by Joachimo Camerario of Nurnberg. At that time it was recommended for diseases of the head and nerves and for trembling of the limbs.

De Jong and Schaltenbrand,[3] by administering doses of 200 mg. of bulbocapnin subcutaneously, found that it stopped the tremor of paralysis agitans. The duration of its effect when given subcutaneously is from

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* From the Department of Neurology and Neuropathology, Harvard Medical School.

* Read at the Fifty-First Annual Meeting of the American Neurological Association at Washington, May, 1925.

1. De Jong, H.: Nederl. Tijdschr. v. Geneesk., January, 1923.

2. Frölich and Meyer: Ueber Dauerverkürzung der gestreiften Warmblutermuskeln, Arch. f. exper. Pathol. u. Pharmakol. **87**:173, 1920.

3. De Jong, H., and Schaltenbrand, G.: Die Wirkung des Bulbocapninns auf Paralysis Agitans und andere Tremorkranke, Klin. Wchnschr. **3**:2045 (Nov. 4) 1924.

three to six hours. De Jong has given it to patients over a period of several months, with no untoward effect, and has not found it to be cumulative.

If given to a cat in doses of 40 mg. per kilogram of body weight, the cat goes into a typical "fixed posture" within about ten minutes. It may be set up on its haunches with its forepaws against a support and will remain in that position for several hours. Voluntary motion

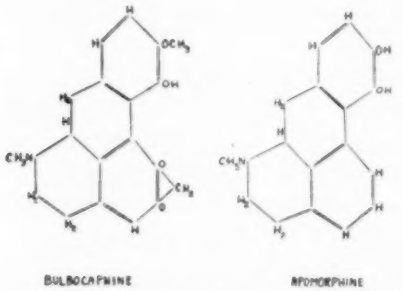

Fig. 1.—Chemical composition of bulbocapnin and apomorphin.

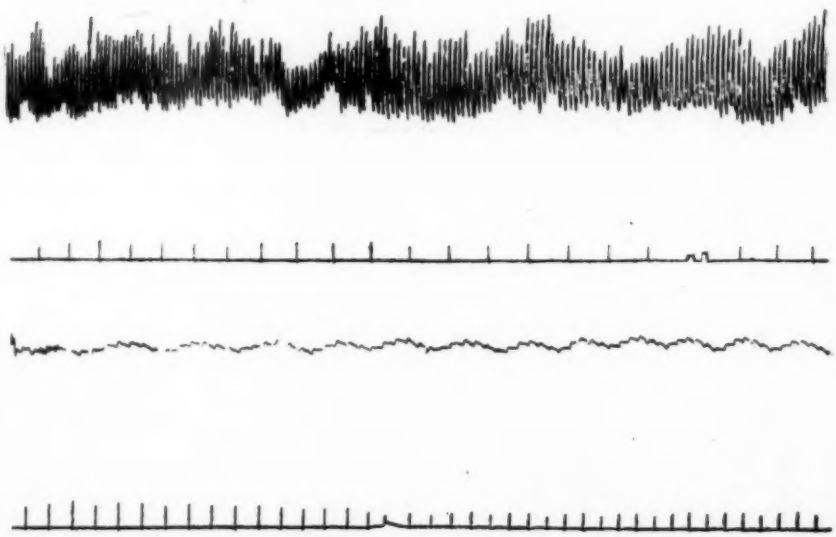

Fig. 2.—Upper line indicates tremor before injection of bulbocapnin; lower line shows cessation of tremor after injection.

ceases, the cat being unable to move its fore legs back to the floor of the cage. The animal can be bent like a piece of lead pipe. Should the dose be increased above 40 mg. per kilogram of body weight, clonic and tonic convulsions follow, and death ensues. With the ordinary dose, it recovers its normal motor activities and shows no effect from the drug after from twelve to eighteen hours.

The effect of this drug on the tremor of paralysis agitans is striking. An elderly man was chosen from the wards of the Binnen-Gasthuis. His right arm, which showed the most tremor, had a pelotte strapped to it over the thenar eminence, and the amplitude of the tremor registered on a kymograph. The upper line on Figure 2 is a record of the tremor before injection. The lower line is a record made twenty-four minutes after the injection of 200 mg. of bulbocapnin subcutaneously, showing a cessation of the tremor with only a pulse tracing. No tremor could be found on examination of the patient twenty-four minutes after the injection. The effect lasts from three to six hours, then it is necessary to repeat the dose. The drug has been given by mouth, but requires a little

Fig. 3.—Cat under influence of bulbocapnin in "fixed posture."

more time to take effect. I have repeated his experiments, and the accompanying protocol and Figure 3 illustrate as well as is possible without the moving picture film, the effect of the dose producing the catatonic-like syndrome.

PROTOCOL OF EXPERIMENT

Experimental cat, normal, healthy, weighing 2.25 kg.

3:24 p. m., 90 mg. of bulbocapnin in hot, aqueous solution given subcutaneously.

3:26 p. m., meows loudly.

3:28 p. m., inactive, pupils widely dilated, drooling.

3:30 p. m., on stimulation, gives a peculiar, prolonged cry. On moving its legs, there is a tendency for them to remain in a given position. On passive movement of the head from side to side, it remains fixed.

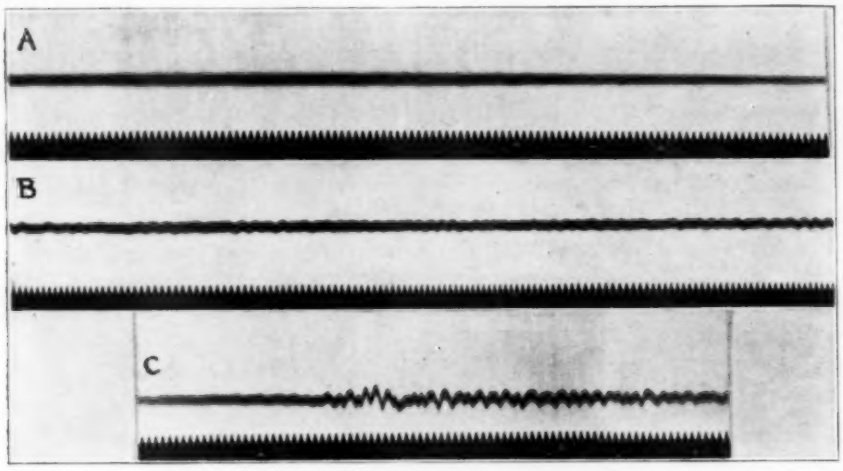

Fig. 4.—Normal electromyogram of cat under influence of bulbocapnin; *A*, leads on tibialis anticus at rest; *B*, leads during slow extension—at height; *C*, leads during quick passive extension.

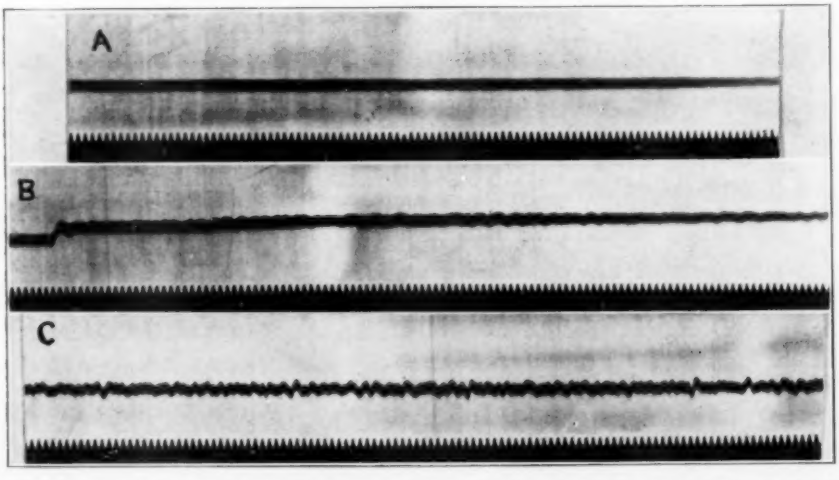

Fig. 5.—Normal electromyogram of cat under influence of bulbocapnin; *A*, leads on gastrocnemius at rest; *B*, leads during passive extension; *C*, leads during passive flexion—at height.

3:32 p. m., feet remain in any position in which they are placed if rested against the floor or side of the cage.

3:35 p. m., retains position in which placed two minutes previously.

3:40 p. m., retains plastic condition.

3:43 p. m., cat placed in upright position with forepaws resting against side of cage, remains fixed.

3:53 p. m., remains at side of cage.

5:22 p. m., cat is in same position.

5:30 p. m., placed on floor of cage.

8:10 p. m., meows loudly, squats on all four feet.

8:15 p. m., when placed against side of cage with claws of front legs sticking into wires of cage, animal remains in fixed position.

11:05 p. m., meows persistently; remains in place against side of cage; slight lateral movement of head is observed; if head is turned to right or left it does not come back to the middle line; cat is placed on its belly with the forepaws extended, but legs are slowly drawn up, and cat comes into a position of rest, where it remains.

Next day, a. m., when animal is set on haunches and forepaws are placed against side of cage it remains in position for about four minutes, after which it slumps into a position of rest on the floor of the cage.

Same in afternoon.

Next day, a. m., animal normal.

De Jong, with Wertheim Salomonson, found a characteristic grouping of the action currents in his electromyograms on experimental animals. I injected into an animal 40 mg. of bulbocapnin per kilogram of body weight and turned it over to Dr. Alexander Forbes of the Department of Physiology of Harvard Medical School, who kindly made the accompanying electromyograms for me. These electromyograms are perfectly normal, and the drug apparently had no effect on the muscles.

SUMMARY

Bulbocapnin will cause a cessation of tremor in many cases of paralysis agitans. The treatment is palliative, but not curative.

The experimental work on animals seems to indicate that bulbocapnin may also be of value in the experimental study of catatonia.

DISCUSSION

DR. SMITH ELY JELLIFFE, New York: I have been very much interested in these experiments of Dr. De Jong. I saw some of the early experiments, and I have read with a great deal of interest his and other reports. The last most extensive report, which is very well worth reading (it is written in English), appears in the *Therapie Beiheft of the Psychiatrische en Neurologische Bladen*, which is the official organ of the Amsterdam Neurological Society. Here Dr. De Jong reports a number of experiments, and therapeutic efforts with paralysis agitans, multiple sclerosis and a number of tremors of the nature that he has already discussed. In general, the paralysis agitans results were not encouraging.

On the botanical side, a few points might be mentioned. We have in this country plants closely related to the Corydalus from which the bulbocapnin is derived. Our *Corydalus glauca,* is widespread throughout the northern part of this country in comparatively high altitudes. *Corydalus glauca* might be used for obtaining the alkaloid. We have other species *Corydalus.*

We have also a plant known as squirrel corn, which belongs to the same family, and a number of related alkaloids have been obtained from *Dicentra cucullaria,* but so far as I know, no pharmacologic experiments have been made on them. They are closely related to the Poppy family botanically and it may be that some of the alkaloids belong in the morphin series.

The psychic component is only one of the many in the activity of the body as a whole, and when certain components in the cortex are cut off and cortical or so-called psychic activities prevented, there results a reduction of the individual to lower forms of functional activity, as, for instance, is seen in the cat. We can expect these so-called catatonic attitudes which are closely related to the decerebrate attitudes of Sherrington, Magnus and Klein and others. But a catatonic motor attitude is not to be confused with the lightly complicated nosologic conception originally outlined by Kahlbaum as "catatonia." As one button does not constitute a suit of clothes, so a motor symptom should not be held equivalent to a disease abstraction.

Dr. Lewis J. Pollock, Chicago: Is there any evidence of influence on the autonomic nervous system such as we see in states of rigidity associated with the sequela to epidemic encephalitis? For example, sialorrhea, etc. When you conclude that it is impossible for the peripheral mechanism to be involved because the rigidity is not influenced by the injection of cocain into the muscle, would it not equally as well speak against the central origin, as the posterior root section would diminish rigidity in paralysis agitans?

Dr. Hugo Mella: As to what becomes of the psychogenic factor in catatonia, we know that if we paralyze a peripheral nerve mechanically, that is, with alcoholic injection, or even if we sever it, we may have a complete paralysis of a limb. At the same time, we see so-called functional paralyses of arms with motor paralysis, so I do not think that rules out the psychogenic activity in catatonia. I felt this was another means of producing a syndrome somewhat similar to it.

As to whether or not it affects the peripheral nerve, I cannot say. We do not know enough about it yet. Contraction of the bladder frequently occurs, also drooling.

THE PRESENCE OF AN OXYTOCIC SUBSTANCE (POSTERIOR HYPOPHYSIS EXTRACT) IN CEREBROSPINAL FLUID*

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How does the physiologically active substance which is constantly found in the posterior lobe of the hypophysis find its way into the blood stream? In 1908, Herring [1] reported the presence of colloid and hyaline bodies in cats in the pars intermedia and the pars nervosa which he believed passed through the infundibular stalk and into the third ventricle. These bodies appeared to break up into granules before entering the third ventricle. Herring considered this colloid and hyaline material to be the secretion of the gland, produced by the pars intermedia and passed into the pars nervosa by some unknown means.

The question of whether the physiologically active substance, pituitary extract, is the product of the pars intermedia or pars nervosa is beyond the scope of this paper and will not, therefore, be discussed. Assuming that pituitary extract is an internal secretion, is it discharged into the cerebrospinal fluid before entering the blood stream? If Herring's hypothesis is true, the secretion, after being passed into the third ventricle, is dissolved there by the cerebrospinal fluid and then enters the circulation by way of the dural sinuses.

In 1910, Cushing and his associates [2] confirmed the histologic observations of Herring, including the discharge of the hyaline material into the third ventricle. They supported these findings further by physiologic studies. Using concentrated (to one-sixth and one-twentieth original volume) human cerebrospinal fluid, they observed, following its injection into dogs and rabbits, depressor followed by pressor effects, diuresis, smooth muscle contraction and glycosuria. They also observed dilatation of the frog's pupil. They concluded, therefore, that Herring's hypothesis was correct and that pituitary extract was discharged into the cerebrospinal fluid. They found no difference in action between ventricular and lumbar cerebrospinal fluid.

Further histologic studies were made by Edinger [3] and others. This author was able to demonstrate by the injection of Berlin blue and of China ink the presence of pericellular spaces and "Lymphspalten" in the hypophysis as far as the tuber cinereum and which he believed to

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* From the Division of Laboratories, Montefiore Hospital.

1. Herring, P. T.: Quart. J. Exper. Physiol. **1**:281, 1908.

2. Crowe, S. J.; Cushing, H., and Homans, J.: Bull. Johns Hopkins Hosp. **21**:127, 1910. Cushing, H., and Goetsch, E.: Am. J. Physiol. **27**:60, 1910-1911.

3. Edinger: Arch. f. mikr. Anat. **78**:496, 1911.

be the "Sekretbahn." He obtained no evidence to show that the secretion entered the third ventricle. Recently Collin [4] reported that in dogs he was able to trace the colloid bodies through the stalk and as far as the tuber cinereum, and suggested that the secretion acts on the nerve cells of this area.

According to the more recent studies of Hogben and de Beer [5] the occurrence of hyaline material in the hypophysis is not constant. They report that of fourteen cats in which the pituitary glands were serially sectioned, only one was found to contain the hyaline bodies, and in that case they appeared to be the result of degenerative changes. This latter view has been held by others, including Bailey.[6]

Of greater significance are the studies of the physiologic effects of cerebrospinal fluid. A careful examination of the literature on this subject, however, reveals no agreement of results or unanimity of opinion.

The work of Cushing and Goetsch [2] has already been referred to. However, in a repetition of these experiments Carlson and Martin [7] obtained negative results. They injected unconcentrated canine cerebrospinal fluid into dogs but could not demonstrate the presence of a substance which caused a pressor effect or which influenced glucose tolerance.

Cow [8] found that normal cerebrospinal fluid from cats anesthetized with urethan and dogs anesthetized with ether and morphin produced practically no oxytocic or pressor effects, but that such fluid obtained sixty minutes after the intravenous injection of duodenal mucous membrane extract caused a slight increase in blood pressure, contraction of the smooth muscle, diuresis and dilatation of the pupil of the enucleated frog's eye. These various actions were not all observed with any one fluid.

Using dogs anesthetized with ether and then injections of morphin and urethan, Dixon [9] obtained cerebrospinal fluid by puncture of the cisterna cerebellomedullaris. In some cases slight negative pressure was used. According to him such fluids showed every known chemical and physiologic action of pituitary extract. Compared with commercial pituitary extract he found that ten drops of cerebrospinal fluid obtained under the foregoing conditions contained from 1 to 10 mg. of pituitary extract. This author found that pituitary extract injected into the circulation causes an excess of posterior lobe hormone to be secreted into

4. Collin, R.: Compt. rend. Soc. de biol. **91**:1334 (Dec. 19) 1924.
5. Hogben, L. T., and de Beer, G. R.: Quart. J. Exper. Physiol. **15**:163, 1925.
6. Bailey, P.: Ergebn. d. Physiol. **20**:162, 1922.
7. Carlson, A. J., and Martin, L. M.: Am. J. Physiol. **29**:64, 1911-1912.
8. Cow, D.: J. Physiol. **49**:367, 1914-1915.
9. Dixon, W. E.: J. Physiol. **57**:129 (March) 1923.

the cerebrospinal fluid within one minute, this excess disappearing into the circulation within five minutes. Ovarian extract acted similarly. He confirmed Cow's [8] findings relative to the action of duodenal mucous membrane extract.

Dixon [9] also observed that pituitary extract artificially introduced into the cerebrospinal fluid passes rapidly into the circulation and then produces its systemic effects. No work is reported by this author on the effect of cerebrospinal fluid on glucose metabolism, but he states that it depresses hyperglycemia (which it should not do if it contains pituitary extract) and that hypophysial (posterior lobe) deficiency may be a cause of diabetes (mellitus or insipidus?). The fact that the fluids were obtained from anesthetized animals may have a bearing on his results.

Trendelenburg,[10] using cats, was able to confirm Dixon's results. He observed, however, that the concentration of the physiologically active substance in these animals corresponds to $\frac{1}{35,000}$ mg. of posterior lobe extract in 1 c.c. of fluid, as opposed to Dixon's finding. Furthermore, Trendelenburg reported that the cerebrospinal fluid from cats diluted five times retained its oxytocic action, which also is in considerable variance with Dixon's experience that it usually required from 3 to 4 c.c. of dog's fluid (ten drops containing from 1 to 10 mg. of pituitary extract) to elicit contraction of the isolated guinea-pig uterus. In some instances Dixon found even this amount to be inactive.

A clinical observation by Mayer [11] deserves mention at this time. This author injected the cerebrospinal fluid obtained by lumbar puncture in cases of cesarean section into other patients in labor who had uterine inertia. In eight out of ten cases contractions of the uterus were induced and in four they were followed by birth. Mayer believes that the cerebrospinal fluid of patients in labor contains pituitary extract and is responsible for the uterine contractions. The evidence, of course, is insufficient to be of such significance.

Recently Dixon and Marshall [12] reported experimental evidence suggesting that the hypophysis can be activated by the ovaries from pregnant rabbits and sows at or near term.

As has been stated, much negative evidence has also been offered relative to the existence in the cerebrospinal fluid of a substance which possesses the biologic characteristics of posterior lobe extract. The work of Carlson and Martin [7] has already been mentioned. In 1912 Herring [13] reported that he could not demonstrate the presence of pitui-

10. Trendelenburg, P.: Klin. Wchnschr. **3**:777 (April 29) 1924.
11. Mayer, August: Klin. Wchnschr. **3**:1805 (Sept. 30) 1924.
12. Dixon, W. E., and Marshall, F. H. A.: J. Physiol. **59**:276 (Dec.) 1924.
13. Herring, P. T.: Proc. Roy. Soc. **92**:102, 1912.

tary extract in cerebrospinal fluid of either thyroid fed or thyroidectomized cats. He used evaporated fluid which he dried at 37 C. and made into a 1 per cent. solution in Ringer's solution. This was tested for oxytocic and pressor effect and for action on kidney and mammary secretions. This may be especially significant because Herring [1] and also Cushing and Goetsch [2] found that hyaline bodies are present in the posterior lobe of the hypophysis in increased amounts following thyroidectomy.

Oehme and Oehme,[14] using unconcentrated cerebrospinal fluid from normal animals, were unable to demonstrate any oxytocic effect on guinea-pig uterus. They observed some vasoconstriction of the rabbit ear vessels.

Leschke [15] failed to observe any oxytocic or oliguric action with cerebrospinal fluid. He injected from 20 to 30 c.c. of cerebrospinal fluid into human beings. No further details are given.

Wassing [16] likewise obtained negative evidence of an oxytocic principle in cerebrospinal fluid. Perfusion of the leg vessels of the frog did not cause an effect like that produced by pituitary extract.

Kramer,[17] in 1911, and Jacobson,[18] in 1920, studied the hemodynamic effects of cerebrospinal fluid. Kramer used human while Jacobson used both human and bovine cerebrospinal fluids. They found no definite evidence of the presence in these fluids of any substance the hemodynamic action of which would suggest the presence of posterior lobe hormone. Moreover, they observed that the effect is essentially depressor as opposed to the pressor action of pituitary extract. These observations may be of particular significance in the light of our findings that the cerebrospinal fluid from human beings not only has no oxytocic effect on the isolated guinea-pig uterus, but also tends to cause inhibition of the uterine horn contractions.

Abel,[19] in his Harvey lecture (1924), summarizing the evidence relative to the presence in the cerebrospinal fluid of a substance which in its physiologic actions is identical to the active principle obtained from the posterior lobe of the hypophysis, says: "Its correctness will not remain unchallenged as long as it has not been demonstrated that the above named physiological actions (cardiovascular, diuretic, oliguric, respiratory) of posterior lobe hormone are exhibited by the cerebrospinal fluid in addition to oxytocic action."

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14. Oehme, C., and Oehme, M.: Deutsche Arch. f. klin. Med. **127**:261, 1918.
15. Leschke, E.: Verhandl. deutsch. Gesellsch. f. inn. Med. **34**:348, 1922.
16. Wassing, H.: Wien. klin. Wchnschr. **26**:1270, 1913.
17. Kramer, S. P.: Brain **34**:39, 1911-1912.
18. Jacobson, C.: Bull. Johns Hopkins Hosp. **31**:185, (June) 1920.
19. Abel, J. J.: Bull. Johns Hopkins Hosp. **35**:305 (Oct.) 1924.

EXPERIMENTAL WORK

We have studied the oxytocic effect of cerebrospinal fluids obtained by lumbar puncture from various patients in Montefiore Hospital. It is my purpose to report our results.

Twenty-eight fluids obtained from the following twenty-five cases were used: generalized atherosclerosis, twelve; postencephalitic syndromes, five; chronic nephritis, two; chronic cardiac disease, three; paralysis agitans, three.

The fluids in their normal unconcentrated states were kept at 39 C. until tested. Each one was tested within thirty minutes after lumbar tap.

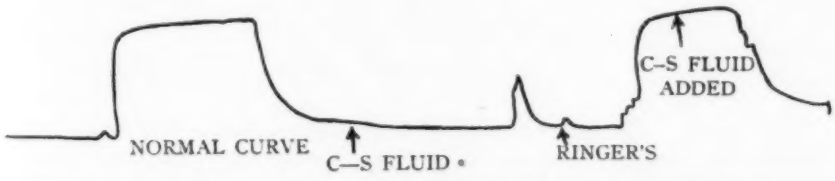

Fig. 1.—The muscle was contracting rhythmically and regularly; the "normal curve" is a typical contraction of this muscle. During relaxation cerebrospinal fluid was added; the relaxation period was thereby prolonged and the succeeding contraction inhibited. Following this the fluid was replaced by Ringer's solution and the normal contraction soon ensued; addition of cerebrospinal fluid during the contraction phase shortened this and hastened relaxation.

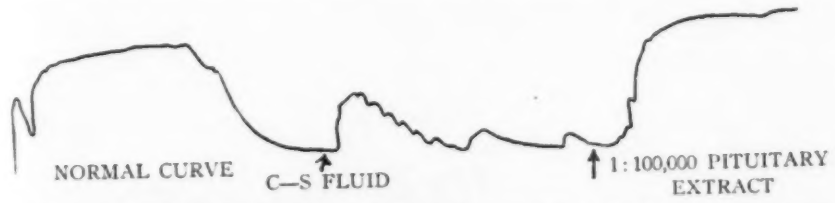

Fig. 2.—Cerebrospinal fluid was added just at the beginning of the normal contraction. The inhibition which is caused is apparent from the curve. This was followed by a prolonged relaxation period during which time the addition of pituitary extract 1:100,000 caused marked contraction.

The muscle used was virgin guinea-pig uterus. This was immersed in Ringer's solution kept at a constant temperature of 39 C.

The following studies were carried out:

1. The normal curves of the muscle in Ringer's solution.

2. The effect of the addition of cerebrospinal fluid during (*a*) the relaxation and (*b*) the contraction phase of the muscle.

3. The determination of the amount of commercial pituitary extract necessary to overcome the inhibitory influence of cerebrospinal fluid.

4. A comparison of the effect of cerebrospinal fluid obtained before with that within three minutes after the intravenous injection of 0.5 c.c. of commercial pituitary extract.

5. Six fluids were tested both in the fresh state and after standing at 39 C. for one and two hours. In addition, in five of these fluids pituitary extract, 1 : 10,000, was added to equal parts of the fluid and allowed to stand at 39 C. for one hour.

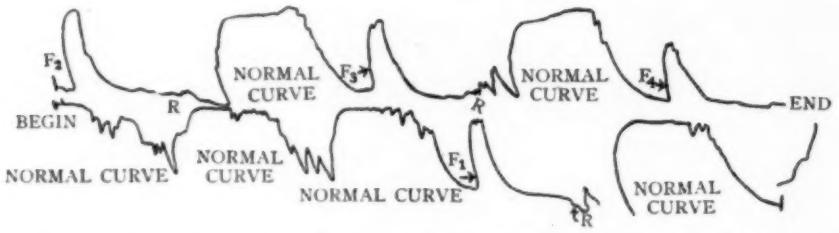

Fig. 3.—The effect of cerebrospinal fluid removed before and within three minutes after intravenous injection of pituitary extract. At F_1 and at F_3, cerebrospinal fluid obtained before pituitary extract injection from two respective cases was added. At F_2 and F_4, cerebrospinal fluid obtained from the same cases respectively after pituitary extract injection was added. At R fluid was replaced by Ringer's. It is apparent that cerebrospinal fluid removed before and after pituitary extract injection caused the identical change; namely, inhibition of the uterine contractions.

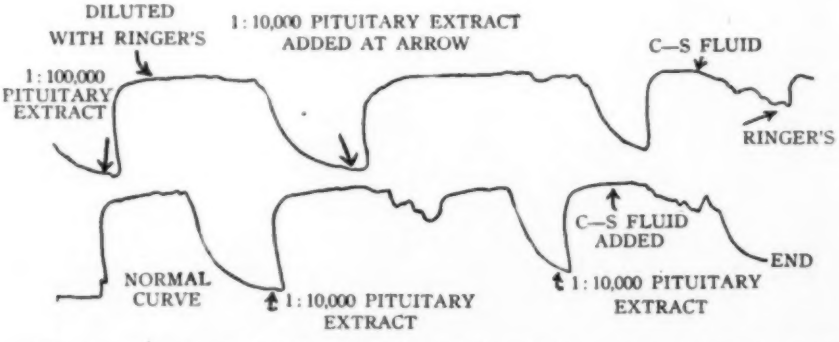

Fig. 4.—The effect of adding Ringer's solution during contraction of the muscle caused by 1 :10,000 pituitary extract. No change was observed. This can be compared with the inhibitory effect following the addition of cerebrospinal fluid at the same stage of contraction. The replacing of this latter fluid with Ringer's solution caused prompt resumption of the regular contractions of the muscle. The cerebrospinal fluid inhibited the action caused by the addition of 1 :10,000 of the pituitary extract preparation used in this instance.

We found that the addition of cerebrospinal fluid during relaxation of the isolated guinea-pig uterus did not cause the sudden and maximal contraction characteristic of posterior lobe extract. No such contraction was observed with any of our fluids. Moreover, there usually occurred

a prolongation of the relaxation period, and when the next contraction occurred it was decidedly diminished in both amplitude and duration, as compared with the normal contraction for that particular segment of the uterus. The addition of cerebrospinal fluid during the contraction phase shortened the duration of this period and hastened relaxation.

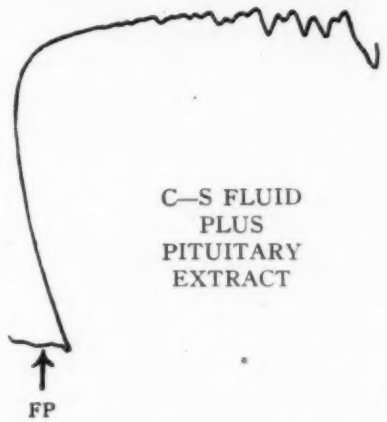

Fig. 5.—This tracing and Figure 6 show two different fluids to which two different preparations of pituitary extract 1 : 10,000 were added. In these cases the cerebrospinal fluid did not alter the action of the pituitary extract in this concentration.

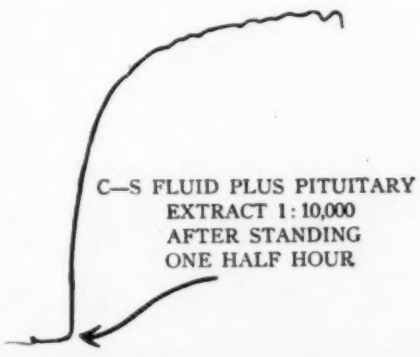

Fig. 6.—This tracing shows in addition that the pituitary extract effect was retained after being mixed with an equal amount of cerebrospinal fluid and allowed to stand for one half hour at 39 C.

We found that cerebrospinal fluid would inhibit the effect of pituitary extract in a concentration of between 1 : 100,000 and 1 : 10,000. This was inconstant as a result of the great variations in the strength of commercial preparations, the sensitivity of the muscle strips and the inhibitory effect of the fluids.

Allowing fluids to stand for one hour at 39 C. did not alter their action on guinea-pig uterus. A mixture of commercial pituitary extract with equal parts of cerebrospinal fluid, kept at 39 C. for one hour, still retained the typical action of pituitary extract on the guinea-pig uterus

COMMENT

The theory that the physiologically active substance constantly found in the posterior lobe of the hypophysis is secreted into the third ventricle where it is dissolved by the cerebrospinal fluid and by means of which it enters the blood stream is founded chiefly on the histologic observations of Herring. However, according to the more recent studies already referred to, it appears that the colloidal bodies described by Herring may not represent the secretion but may be accidental constituents to be found in the hypophysis under certain (degenerative?) conditions. Moreover, these bodies appear not to be present in elasmobranchs.[20] It may also be of significance to point out that there is no counterpart in the body of a substance so powerful and widespread in its actions being subjected to such a circuitous route to find its way into the circulation.

Abel has concentrated the active principle of the hypophysis to a degree at which it produces an oxytocic effect in a dilution of 1 in 18 millions or more, at which it causes a pressor effect in cats in doses of 0.01 mg. or less, and at which it produces the characteristic respiratory effects in dogs and rabbits. Therefore, it appears that all these actions are caused by one and the same substance, because, as Abel points out, it is highly improbable that in such great dilution several active substances are present. Abel asserts further that there is no principle which causes any one of these actions alone. Consequently, in order that the presence of posterior lobe extract be demonstrated, it is essential that the material exhibit all of these actions. Our failure, therefore, to obtain positive evidences of oxytocic action by any of our twenty-eight fresh unconcentrated cerebrospinal fluids speaks strongly against the presence of an active posterior lobe extract in these fluids, under the conditions in which they were obtained, in sufficient concentration to cause such oxytocic effect.

The observation of an inhibitory action of spinal fluid on the isolated guinea-pig uterus may be of great physiologic significance. The fact that cerebrospinal fluid is practically a physiologic sodium chlorid solution [21] adds to the value of this finding. We repeatedly observed that the addition of an amount of Ringer's solution equal to the volume of cerebrospinal fluid that was added did not alter the action of the uterus. Our observations, therefore, support the findings of Jacobson [18]

20. Herring, P. T.: Quart. J. Physiol. **4**:183, 1911.

21. Halliburton, W. D.: Proc. Roy. Soc. Med., Section of Neurology, 1916.

and Kramer [17] that the hemodynamic effect of cerebrospinal fluid is essentially depressor as opposed to the pressor action of posterior lobe extract. If quantitative constancy should be found to occur in the depressor or anti-oxytocic action of normal cerebrospinal fluids, it may possibly be utilized as a means for comparison of fluids from different types of cases in which the central nervous system (especially the choroid plexus) may be involved.

Our results do not confirm Dixon [9] that pituitary extract introduced intravenously causes a sudden increase in the posterior lobe hormone content of the cerebrospinal fluid. He claimed that this excess disappeared from the fluid into the blood after five minutes. Our fluids were obtained within three minutes after the intravenous injection.

We observed no alteration in the action of cerebrospinal fluid on the isolated guinea-pig uterus after permitting the fluid to stand at 39 C. for one hour. This overcomes the possibility of an oxytocic principle having been present but having been destroyed by reason of alterations in the hydrogen ion concentration [22] or by the action of ferments which may have been present in small amounts.[23] We obtained evidence significant of a neutralizing action of cerebrospinal fluid on commercial pituitary extract in concentration of 1 : 100,000. This was very variable, however.

Although we constantly obtained negative results in the experiments herein reported, nevertheless our work does not exclude the possibility that the physiologically active substance found in the posterior lobe may be poured into the third ventricle and be carried by the cerebrospinal fluid to the blood stream, at least under certain at present unknown conditions.

There is also the possibility that the oxytocic principle may have been present in the spinal fluid in too great a dilution to cause an effect on the isolated guinea-pig uterus. We have been able to obtain typical pituitary extract action on a uterine segment by using commercial pituitary extract in a dilution of 1 : 300,000, but observed no such muscle contraction after adding 3 c.c. of fresh spinal fluid. On the contrary, the fluid caused inhibition of uterine contraction, as has already been described. Assuming that there was 0.01 mg. of active posterior lobe extract present in 1 c.c. of this liquid at the time the spine was tapped, 3 c.c. should have caused an oxytocic effect.

The criticism might be offered in our work, as in some others, that we used pathologic fluids. However, by reason of the variety of cases from which we obtained our material and, moreover, because of the constancy of our findings, we are of the belief that this objection has been overcome.

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22. Adams, H. S.: J. Biol. Chem. **30**:235 (June) 1917.
23. St. Draganescu and Lissievici-Draganescu: Biochem. Ztschr. **156**:460, 1925.

SUMMARY

Of twenty-eight cerebrospinal fluids obtained from twenty-five different patients, none caused an oxytocic effect on the virgin guinea-pig uterus. On the contrary, we observed a tendency of these fluids to inhibit contraction of the isolated uterus of the guinea-pig. We failed to obtain evidence to show that the intravenous injection of pituitary extract causes an increased secretion of the active principle present in the posterior lobe of the hypophysis into the cerebrospinal fluid within three minutes after the injection.

TOXEMIAS OCCURRING IN THE EARLY STAGES OF MENTAL DISEASE*

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CINCINNATI

Careful examination of patients in the acute stages of the various psychoses so commonly reveals clinical evidence of systemic toxemia, fever, delirium and delirioid states, indicanuria, albuminuria, leukocytosis and the like that they hardly need comment. Three years ago, we undertook a systematic search for evidence of systemic intoxication of a bacterial or metabolic nature. Our opportunities for the study of the acute phases of mental disease are exceptionally good, as the Longview Hospital receives the majority of the acute mental cases from a population of over half a million people, many of the patients coming during the earliest stages of their disease.

All examinations have been begun on the day of admission, and practically all have been completed by the following morning. The patients are received in the morning, and most of them have had breakfast before admission. They are placed at rest in bed, no food being given except water. Before the evening meal, after a ten or twelve hour fast, the specimens of blood for examination are taken.

Chemical examination of the blood originally included quantitative determination of the nonprotein nitrogen, urea nitrogen, uric acid, creatinin and sugar, together with determination of the carbon dioxid combining power of the plasma. We soon found that the urea nitrogen and the carbon dioxid combining power of the plasma yielded the most valuable information. In this paper we propose to discuss chiefly these two items. To a less extent we will consider the leukocyte count, the uric acid and the creatinin of the blood. Clinically, the determination of the carbon dioxid combining power is not as conclusive as is that of the urea nitrogen of the blood, because it is subject to more variables than is the urea nitrogen.

Mild acid intoxications are extremely frequent in patients when they are admitted to the hospital. These can be easily explained on the basis of muscular exertion with fatigue, excitement with fatigue or starvation from the failure to eat regularly. Nearly all toxic psychoses show a marked depletion of the carbon dioxid combining power, usually with

* From the Research Department of Longview Hospital.

urea retention. Several explanations are possible: excitement with fatigue; impairment of kidney function by the toxin causing the psychosis, with a resulting failure of the kidney to excrete the acids of normal metabolism; the fact that the toxin produced may be an acid and its presence in the blood will lower the alkali reserve. The last alternative is certainly true in those cases in which a brilliant therapeutic result is obtained by giving alkali.

The normal values lie within the following limits: urea nitrogen, from 11 to 15 mg. per 100 c.c. of whole blood; uric acid, from 0.8 to 3 mg. per 100 c.c. of whole blood; carbon dioxid combining power of plasma, from 53 to 77 c.c. reduced to 0 C. and 760 mm. pressure, bound as bicarbonates by 100 c.c. of plasma in adults. We consider as pathologic: urea nitrogen, 20 mg. or more per 100 c.c. of whole blood; uric acid, 4 mg. or more per 100 c.c. of whole blood; carbon dioxid combining power of plasma, 52 c.c. or lower.

We have employed Folin's system of blood analysis for urea nitrogen, dextrose, uric acid and so forth, and the method of Van Slyke and Cullen for the determination of the alkali reserve.

REPORT OF CASES

CASE 1.—A woman, aged 33, was admitted to the hospital in a state of acute hallucinatory confusion; she was not well oriented for time or place, was euphoric and obscene, sang and shouted a great deal, was restless and excited and had to be restrained. She had hallucinations both of sight and hearing. Her appendix had been removed two weeks, and her tonsils shortly before admission.

Blood Examination.—The results of the blood chemical examination are shown in Chart 1. The figures on admission were: urea nitrogen, 50 mg.; uric acid, 10 mg.; carbon dioxid combining power, 40 c.c. These figures indicate nitrogen retention and acid intoxication. The urine examination disclosed large amounts of acetone, diacetic acid and indican.

Treatment and Course.—The treatment consisted of bed rest, Fischer's solution by rectum, plenty of fluids and a milk diet. A second blood chemical examination, forty-eight hours later, showed normal findings: urea nitrogen, 15 mg.; uric acid, 1.5 mg., and carbon dioxid combining power, 62 c.c.. Coincident with the improvement in the toxic condition there was a striking improvement in the mental symptoms. The patient had become normal mentally.

From the standpoint of descriptive psychiatry, the diagnosis in this case would have been acute delirious mania. From the blood chemical standpoint, however, it was an acute toxic psychosis of unknown origin. There had been no recurrence of the disease in the next two years.

CASE 2.—A woman, aged 21, was admitted to the hospital Feb. 28, 1924, in a state of acute hallucinatory confusion. The onset had been sudden, one week before admission. The patient was not oriented for time or place; she showed echolalia and perseveration to a marked degree and had hallucinations of hearing and her general mental content was decidedly manic in trend. She had given birth to a baby five months before and had nursed the child until a week prior to administration. She had been subject to attacks of grand mal since child-

hood, although she had never previously shown any psychotic attacks. She was of average intelligence, although she had not attended school regularly because of her epileptic attacks. The physical examination was negative as far as gross findings were concerned.

Laboratory Examination.—This disclosed a polymorphonuclear leukocytosis together with the following blood chemical findings shown in Chart 1: on admission, urea nitrogen, 64 mg.; carbon dioxid combining power, 35 c.c.; forty-eight hours later the corresponding figures were 15 mg. and 66 c.c.

Treatment and Course.—The treatment consisted of the administration of alkali, dehydration, hot packs and continuous baths. On March 4, the patient was well mentally. She remained in the hospital until April 4, 1924, when she was sent home on a trial visit; she was discharged from the outpatient clinic a year later without recurrence of the psychosis. This case may be interpreted as an acute toxic psychosis occurring in the puerperium.

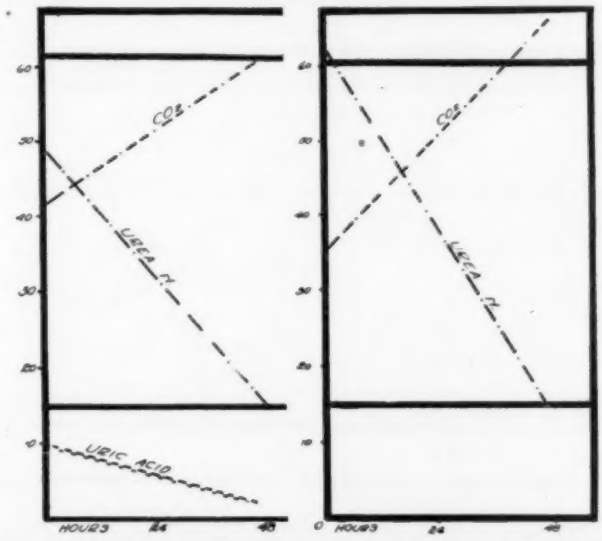

Chart 1.—Blood chemistry findings in Case 1 (left) and Case 2 (right). Carbon dioxid combining power of plasma, normal level 62.

CASE 3.—A man, aged 25, was admitted to the hospital Oct. 30, 1924, in a state of acute hallucinatory confusion. The patient had recently come to America from Germany. He was an electrician and had worked as a technical assistant in several physicochemical and roentgenographic laboratories in Berlin. He was married, and his personal and family history was negative for nervous and mental disease. The attack of confusion had been ushered in by a mild depression, which was ascribed to nostalgia. At the time of admission the patient was greatly confused and had hallucinations of hearing. Physical examination revealed a generalized twitching of the muscles such as is seen in impending uremia.

Blood Chemistry.—The findings, illustrated in Chart 2, are given in Table 1. The figures on admission disclosed nitrogen retention. Elimination by means of dehydration and hot packs restored the blood chemistry to normal on the thirtieth day after a rather severe colonic stasis was removed by enemas. By this time the patient was entirely well mentally, and he has remained well since.

TABLE 1.—*Blood Chemistry Findings in Case 3*

Time	Urea Nitrogen	Carbon Dioxid Combining Power
On admission	25 mg.	56 c.c.
Fifth day	30 mg.	59 c.c.
Fourteenth day	20 mg.	56 c.c.
Thirtieth day	12 mg.	64 c.c.

CASE 4.—A negro girl, aged 21, whose personal and family history is unimportant, was admitted to the hospital April 22, 1924, in a state of pronounced catatonia with waxy flexibility and mutism. The diagnosis of catatonic dementia praecox had been made by several psychiatrists prior to admission. Physical examination disclosed severe endometritis. The blood pressure was extremely low, registering 70 mm. systolic and 50 mm. diastolic. Daily observations of the blood pressure showed that it remained at this low level until the time of her discharge 120 days later, when it had risen to 90 mm. systolic and 60 mm. diastolic.

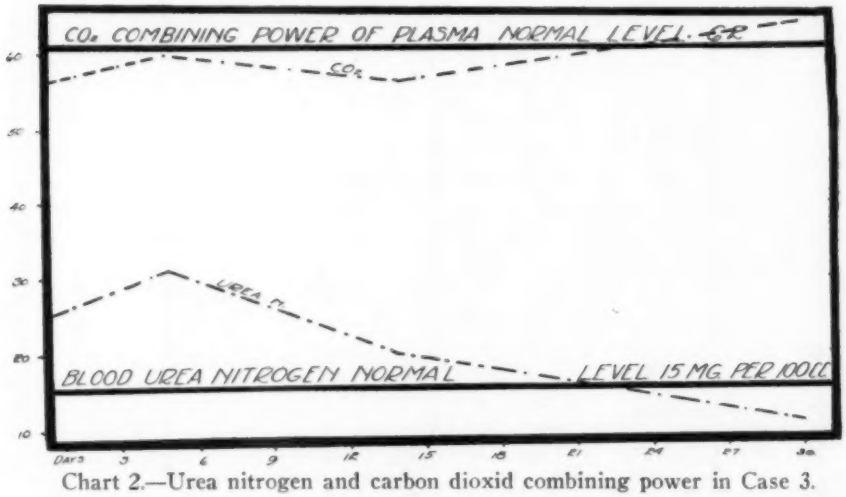

Chart 2.—Urea nitrogen and carbon dioxid combining power in Case 3.

Blood Examination.—The laboratory examination on admission (Chart 3) revealed a polymorphonuclear leukocytosis of 19,000, and urea nitrogen, 23 mg. One hundred and twenty days later the leukocyte count was 6,000, and the urea nitrogen 12 mg.

Treatment and Course.—Treatment was directed toward the infected pelvic condition, and the patient was given a long course of hydrotherapy. She was sent out on a trial visit 120 days after admission when she was mentally well. She was discharged from the outpatient clinic one year later without recurrence of the mental trouble.

CASE 5.—A white woman, aged 45, was admitted to the hospital Aug. 31, 1924, in a state of manic excitement after she had made a threat of homicide. She had no delusions or hallucinations. She had suffered an attack of depression four years before in which she was confined in a hospital after threatening suicide. She has been subject to unusual fluctuations of affect since childhood, but only two of the attacks were severe enough to warrant commitment. At no time has she shown any confusion, hallucinations or delusions. Physical examination

revealed nothing of importance except that panhysterectomy had been performed some years before.

Blood Chemistry.—The results of this examination, shown in Chart 4, on admission were: urea nitrogen, 30 mg.; carbon dioxid combining power, 40 c.c. Nine weeks later the corresponding figures were 15 mg. and 51 c.c. On admission, there were evidences of nitrogen retention and acid intoxication. The patient recovered from her manic attack in nine weeks, and the blood chemistry came within normal limits.

CASE 6.—A white man, aged 55, a building contractor, was admitted to the hospital Aug. 1, 1922, in a state of manic excitement. He was euphoric, with grandiose delusions of great wealth. A tentative diagnosis of general paralysis was made, but the neurologic, blood and spinal fluid examinations gave entirely negative findings. He remained in a manic state for two months and then

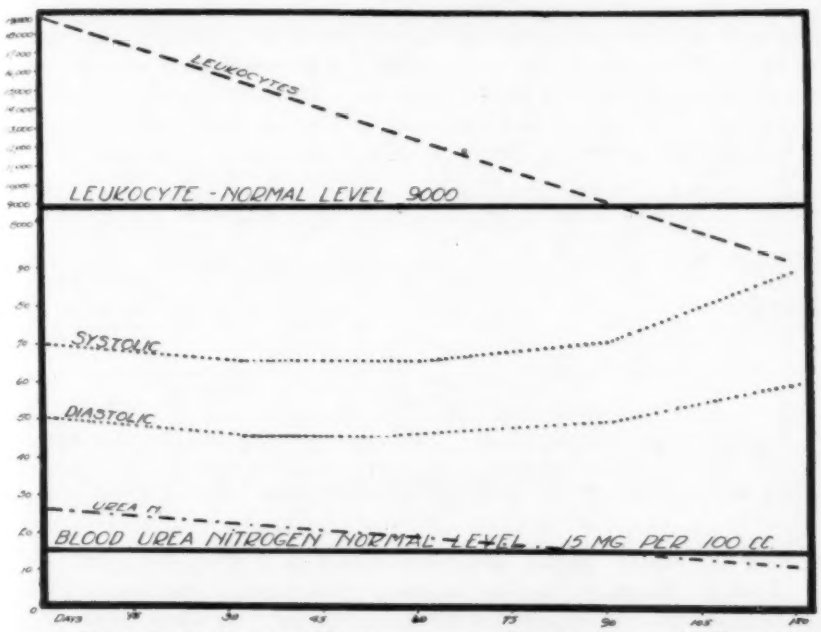

Chart 3.—Leukocytes, blood pressure and urea nitrogen in Case 4.

recovered completely. He was returned to the hospital July 26, 1924, in practically the same condition as before, a diagnosis of general paralysis having been made by a number of psychiatrists. The neurologic, blood and spinal fluid findings were again negative, except that the patient had occasional attacks of divergent strabismus with double vision. At this time it was learned that before his previous attack he had had an operation on his nose, and following this had lain in a stuporous state for over two months. At the time of the physical examination he was greatly underweight. Stereoscopic plates of the skull showed a chronic infection of the ethmoid and antrum.

Blood Chemistry.—At the time of his second admission, blood chemical examination showed nitrogen retention and lowering of the alkali reserve.

The figures, illustrated in Chart 4, are given in Table 2.

Course.—The patient recovered from the manic attack in eleven weeks, gained greatly in weight and the blood chemistry returned to normal. The patient was sent out on a trial visit Jan. 2, 1925, and has remained well since, attending to his affairs in a capable manner.

CASE 7.—A girl, aged 19, was admitted to Longview, Sept. 23, 1924, in a condition of acute manic excitement. The attack had begun about a week before.

Blood Examination.—On admission, there was a leukocytosis of 15,000; the urea nitrogen was 35 mg., and the carbon dioxid combining power was 40 c.c.

Course.—Fluids and salt solution were given for three days, in addition to a milk diet. On the third day, the blood examination was unchanged. Alkalis were added, and then the carbon dioxid combining power rose and the urea nitrogen fell to normal. A further examination, thirty-six days after admission, showed leukocytes, 6,000; carbon dioxid combining power, 61 c.c., and urea nitrogen, 14 mg. These figures are illustrated in Chart 5. The physical condition of the patient has greatly improved, but mentally there is still a state of manic excitement though it is not so marked as on admission. The temperature during the acute phase of the attack ranged from 101 to 103 F. While this patient has improved, the improvement has not been so marked as in the two other cases reported.

Comment.—This case is interesting from the blood chemical standpoint. We interpret nitrogen retention in terms of kidney impairment, the cause of which

TABLE 2.—*Blood Chemistry Findings in Case 6*

Time	Urea Nitrogen	Carbon Dioxid Combining Power	Body Weight
On admission	31 mg.	39 c.c.	100 lbs.
Eighth week	18 mg.	44 c.c.	140 lbs.
Eleventh week	16 mg.	53 c.c.	150 lbs.

has been assigned to acid intoxication by Dr. Martin H. Fischer. Others have said that the kidneys fail to excrete acids. In this case, however, the kidney functions did not improve until alkali had been added to the regimen. This is in favor of the view of Dr. Fischer that the acidosis suppressed the kidney function.

CASE 8.—A colored woman, aged 65, admitted to Longview Hospital in a state of manic excitement, had had an attack of depression four years before, followed by a lucid interval, which in turn was followed by a manic attack. She was euphoric and talkative. She passed from a state of wild excitement to one of delirious mania when she was admitted to Longview Hospital. Large quantities of green pus were pouring from her nose. The patient also coughed up large quantities of this same green pus, which proved on bacteriologic examination to contain large quantities of gram-positive diphtheroid bacilli.

Blood Examination.—On admission there was a nitrogen retention of 25 mg. with an acid intoxication, the carbon dioxid combining power being 44 c.c. There was also a leukocytosis of 14,000. The findings are shown in Chart 6.

Treatment and Course.—The treatment consisted of Fischer's solution by rectum, and liquid diet when the patient could be induced to take nourishment. Forced feeding was resorted to on two occasions but was abandoned because the patient showed signs of circulatory collapse on both occasions. She became steadily worse. On the eighteenth day the urea nitrogen was 50 mg.; carbon dioxid combining power, 45 c.c., and leukocytosis, 16,000.

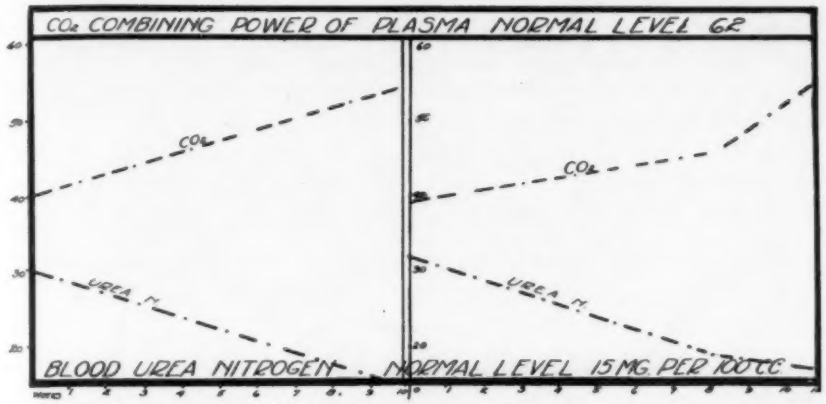

Chart 4.—Carbon dioxid combining power and urea nitrogen in Case 5 (left) and Case 6 (right).

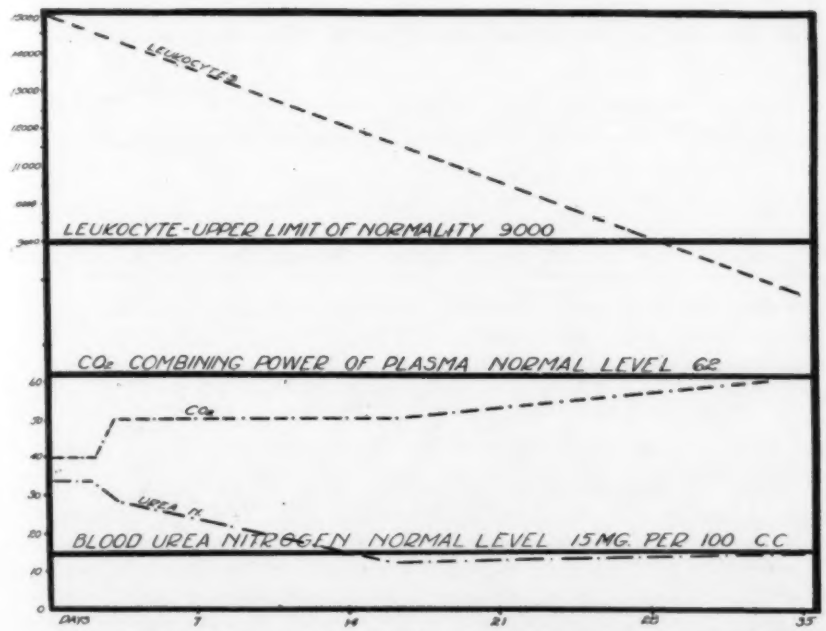

Chart 5.—Leukocytes, carbon dioxid combining power and urea nitrogen in Case 7.

Both antrums were washed out, a large amount of foul smelling pus being obtained from the left side. After this, the patient improved greatly both mentally and physically. Sixty days after admission, blood chemical examination revealed urea nitrogen, 12 mg.; carbon dioxid combining power, 62 c.c.; leukocytes, 9,000. The temperature, which had ranged from 102 to 104 F., had returned to normal. The patient continued to improve, gained weight and was sent home mentally well four months after admission.

Case 9.—A white man, aged 35, when admitted to the hospital Aug. 21, 1924, was euphoric and confused, and showed considerably increased psychomotor activity. He sang and talked a great deal, made rhymes and showed the flight of ideas and faulty perception common to the manic phase of manic-depressive insanity. His family and personal history were negative for nervous or mental disease.

Laboratory Examination.—On admission, nitrogen retention, acidosis and polymorphonuclear leukocytosis were disclosed.

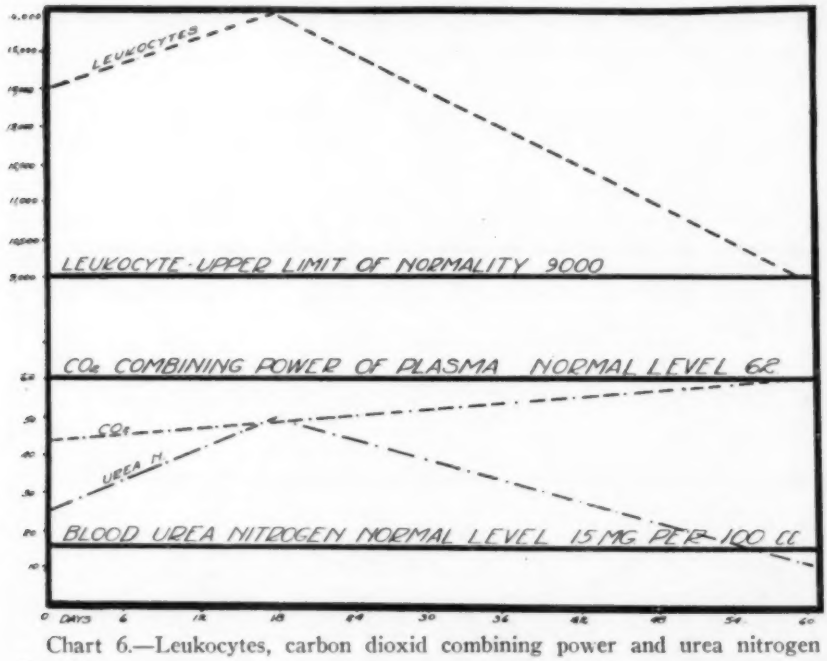

Chart 6.—Leukocytes, carbon dioxid combining power and urea nitrogen in Case 8.

Treatment and Course.—Treatment consisted of alkali, dehydration and hydrotherapy in the form of hot packs and continuous baths. The patient improved greatly during the first three weeks of treatment. His confusion cleared, he became oriented and gave a clear account of himself. He stated that he had been drinking before admission. However, it is questionable whether alcohol was the cause of his symptoms.

The fourth week after admission the patient began to show considerable clouding of consciousness, in which state he remained until sent out on a trial visit, Dec. 12, 1924. Since then, he has improved slowly although he still has some confusion at times. The course of the blood chemistry is shown in Chart 7 and in Table 3.

TABLE 3.—*Blood Chemistry Findings in Case 9*

Time	Urea Nitrogen	Carbon Dioxid Combining Power	Leukocytes
On admission	38 mg.	37 c.c.	14,000
Fifth day	28 mg.	59 c.c.	.....
Sixteenth day	12 mg.	57 c.c.	.....
Seventieth day	20 mg.	58 c.c.	11,000

Comment.—It is interesting to note that clouding of consciousness returned with a rise in the urea nitrogen. The patient was mentally clear during the third week when the nitrogen retention disappeared for a time.

CASE 10.—A woman, aged 71, was admitted to the hospital Feb. 17, 1925, in a state of agitated depression with confusion, which had had its onset three months before.

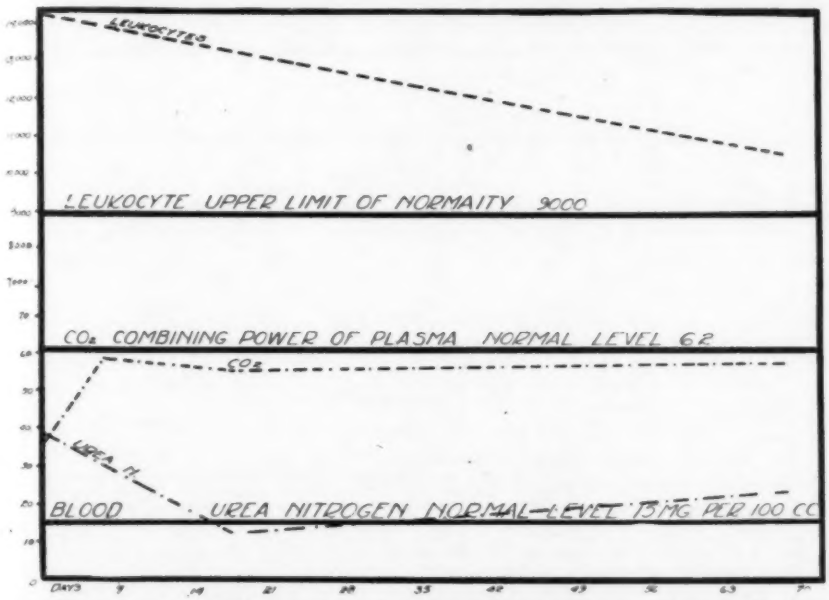

Chart 7.—Leukocytes, carbon dioxid combining power and urea nitrogen in Case 9.

Laboratory Examination.—At the time of admission the blood chemical examination revealed a nitrogen retention of 32 mg. with a lowering of the alkali reserve. The urine contained 2 gm. of albumin per liter and many granular and hyaline casts.

Treatment and Course.—The usual treatment of alkali, dehydration and continuous baths was instituted and in three days the urea nitrogen came down within normal limits, the alkali reserve rose, and the albumin and casts disappeared from the urine. Mentally, the woman had improved greatly, and within two weeks she was well. The course of the blood chemistry is shown in Chart 8 and in Table 4.

Comment.—This case may be interpreted as a psychosis of the depressed confusional type on the basis of an acute exacerbation of chronic nephritis.

TABLE 4.—*Blood Chemistry Findings in Case 10*

Time	Urea Nitrogen	Carbon Dioxid Combining Power
On admission	32 mg.	50 c.c.
Third day	17 mg.	70 c.c.
Thirtieth day	16 mg.	66 c.c.

CASE 11.—A negro man, aged 45, was admitted to the hospital Nov. 11, 1924, in an acute delirious state, with a history of drinking moonshine continuously for the past month. He was violent, and it required four policemen to bring him to the hospital.

Laboratory Examination.—On admission the blood chemistry showed marked nitrogen retention, as well as a lowered alkali reserve.

Treatment and Course.—Alkali and glucose were given but to no avail. The urea and total nitrogen rose steadily, as did the uric acid and creatinin. The

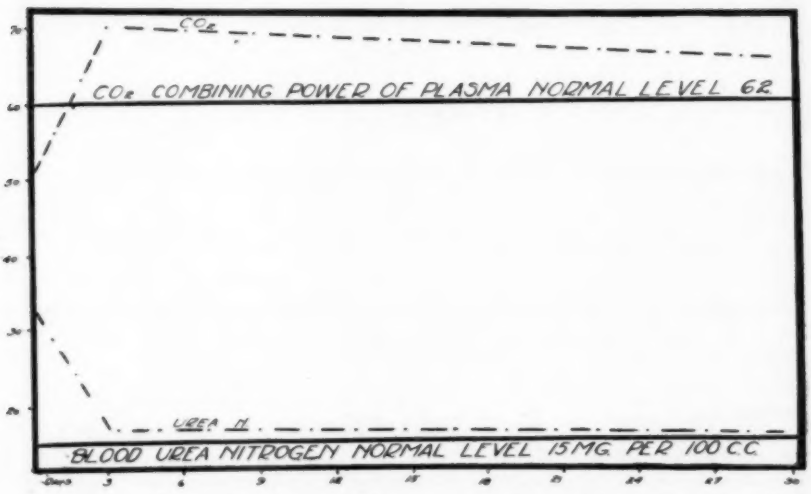

Chart 8.—Carbon dioxid combining power and urea nitrogen in Case 10.

man gradually sank into a comatose condition with fibrillary twitching of muscles, and he died seventy-two hours after admission.

The course of the blood chemistry is shown in Chart 9 and in Table 5.

CASE 12.—A white woman, aged 49, was admitted Aug. 21, 1924, in a state of acute delirious excitement, so violent that it required four nurses to take her to the ward. The history disclosed that she had been depressed for three months before admission and had said on several occasions that she wanted to die. She

TABLE 5.—*Blood Chemistry Findings in Case 11*

Time	Urea Nitrogen, Mg.	Total Nitrogen, Mg.	Uric Acid, Mg.	Creatinin, Mg.	Carbon Dioxid Combining Power, C.c.	Sugar, Mg.
On admission	100	200	10	1.5	40	110
Twenty-four hours	95	190	15	2.5	50	130
Seventy-two hours	100	220	18	4.5	62	170

also had mild persecutory ideas with hallucinations of hearing. One week before admission she complained of dizziness and some dimness of vision. Following this she became disturbed.

Laboratory Examination.—At the time of admission the urine showed 0.75 gm. per liter of albumin and hyaline casts. The blood chemical examination revealed urea nitrogen retention of 60 mg., and carbon dioxid combining power of 28 c.c.

Course.—The temperature rose to 106.6 F., and the patient died forty-eight hours after admission. Here we are evidently dealing with a uremic psychosis.

COMMENT

In the cases described, we see manic-depressive, schizoid and confusional attacks accompanied by signs of systemic toxemia, which disappeared *pari passu* with those signs. Some of the cases were benefited

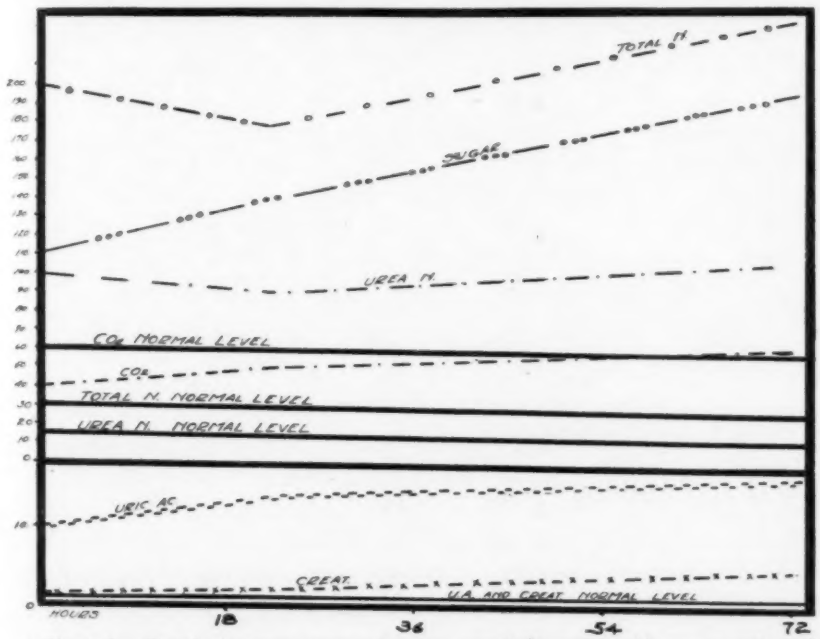

Chart 9.—Total nitrogen, urea nitrogen, creatinin, uric acid, sugar and carbon dioxid combining power in Case 11.

by treatment directed toward the elimination of the toxemia. In other cases, although the signs of toxemia in the blood disappeared, the patients did not improve mentally. These cases were seen late in the course of the disease, and we believe that the damage to the cerebral cells by the toxemia had become irreparable.

In this connection, attention may be called to Dr. Martin H. Fischer's [1] work on fatty degeneration. In brief, he considers the normal brain

1. Fisher, M. H., and Hooker, Marian O.: Fats and Fatty Degeneration, New York, John Wiley & Sons, 1917, pp. 84 and 85. Personal communication to the author.

as a colloid-chemical emulsion of fats in a hydrated colloid, the colloid being protein. In an emulsion, the fat is divided in very minute particles which are so small as to be invisible by means of the ordinary microscope. The emulsion can be broken by any substance that will affect the hydrated colloid. If too much water is added, the colloid is diluted to the point at which it will not be effective in holding the fat in emulsion. If the colloid be dehydrated by appropriate agents, such as alcohol or salts, it can no longer hold the fat in emulsion. Under such conditions, the small, hitherto invisible particles coalesce to form larger particles which now are visible under the microscope.

Being a perfect emulsion, the normal brain under the microscope shows no visible fat particles as they are too small to be seen. However, if this emulsion is cracked or broken by any means similar to those employed in breaking emulsions in vitro, then the invisible fat particles coalesce to form larger particles, the result being that we have the pathologic pictures of lipoid degeneration, fatty degeneration, and fatty infiltration. A common cause of this breaking of the emulsion is acid intoxication, which causes some of the proteins to swell, and others (the globulins) to be dehydrated and precipitated. This combination of swelling and precipitation yields the pathologic picture of cloudy swelling. If cloudy swelling persists, it is followed by fatty degeneration and we have then reached the irreversible point of the reaction. All treatment to be effective must be instituted before this irreversible point is reached.

SUMMARY

1. Evidence is presented to show that manic-depressive, schizoid and confusional reactions may, in their early stages, be accompanied by signs of toxemia: leukocytosis, acidosis, fever and nitrogen retention.

2. Treatment directed toward the elimination of the toxemia is frequently effective in bringing about a mental recovery.

3. The toxins, acid or otherwise, so affect the hydrated colloids of the nerve cell as to bring about a cracking of the emulsion of which the nerve cell is composed. Treatment to be effective must take place before this irreversible cracking point is reached.

THE SPINAL FLUID IN EPILEPSY

A STUDY OF FIFTY CASES *

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Epilepsy is one of those conveniently comprehensive terms, not infrequently found in medicine, that includes a number of different conditions. It is quite natural, therefore, that some difference of opinion should exist in regard to the spinal fluid findings. A large number of investigations have been made of the subject, none of which, however, reveal any specific, pathognomonic condition of the fluid. Boyd [1] reports that, as a rule, there are no characteristic changes in the spinal fluid of epileptic patients. However, he finds a moderate lymphocytosis, with a corresponding increase in globulin, in a relatively high percentage of his patients. These findings and the paucity of recent examinations with newer technical methods seem to justify this study in which a comprehensive examination of the fluid has been attempted.

Fifty cases were selected from some 1,600 epileptic patients; they included a group of twenty-five men and one of twenty-five women, each group being selected with the purpose of embracing the various principal types of epilepsy. At the time of withdrawal of the fluid for examination, sodium phenobarbital was also injected into the spinal canal for therapeutic purposes. By repeated chemical examinations of the fluid at different times after this injection, data relative to the reaction of the system to the injection of this drug were also obtained.

The complete analysis of the fluid consisted of physical, chemical and microscopic examinations, and involved the determination of the intraspinal pressure before and after tap, the hydrogen ion concentration, examinations for albumin and globulin, the cell count, including a differential count, and a quantitative study of urea, sugar and chlorids. The amount of urea and sugar present in the spinal fluid was compared with that present in the blood at the same time. In addition, Abderhalden's ninhydrin reaction and a test for cholin were performed as part of the routine examination. Special stress was laid on colloidal reactions, and in nearly every case Lange's gold reaction was paralleled with the mastic and benzoin curves.

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* From the Craig Colony Laboratory.

* Read before the twenty-fourth annual meeting of the National Association for the Study of Epilepsy, at Richmond, Va.

1. Boyd, W.: The Physiology and Pathology of Cerebrospinal Fluid, New York, the Macmillan Company, 1920.

PRESSURE

To facilitate spinal tap, a chair specially designed by Williamson [2] for the purpose was used and proved very satisfactory. This chair makes it possible to hold resistant patients in a proper position and keep them quiet during the operation. The puncture was done in the upright posture and pressure was measured by means of a mercury manometer which was joined to a platinum-iridium needle by a small rubber tube with metallic connections on either end. It is well known that changes in position create a marked variation in the intraspinal and intracranial pressures. In interpreting the results obtained in pressure readings, consideration must be given to a number of important factors: the type of pressure apparatus used, the insertion of the needle, the respiratory movements and external factors, such as coughing and crying. In the fifty cases, considerable variation in individual pressures was observed. However, there are probably factors that do not allow absolute comparison in all cases. Low values especially ought to be rated with caution, because the slightest mistake in technic as, for instance, the touching of the needle against the anterior wall of the spinal canal, may close the opening in the needle and thus give an incorrect pressure reading.

The average pressure in the fifty cases was 13.9 mm. of mercury, which corresponds approximately to 200 mm. of water. The readings ranged from 6 to 38 mm. of mercury when measured during the interparoxysmal period. In a few cases in which the seizures were severe in character, it was possible to perform lumbar puncture during the convulsions. In these cases, the pressure was increased. In one, the pressure rose from 25 to 50 mm. of mercury. On the other hand, in another case in which the attacks were mild, the pressure was not influenced to any appreciable degree. In one patient, a pressure of 40 mm. of mercury suggested, together with other clinical symptoms and spinal fluid findings, the diagnosis of a brain tumor.

HYDROGEN ION CONCENTRATION

For the determination of the hydrogen ion concentration, a sodium and a potassium phosphate standard solution was used with phenolsulphonephthalein as an indicator. We failed to find in the literature any previous reference to the hydrogen ion concentration of spinal fluid in epileptics. Recent theories of alkalinity and acidosis, as factors in the production of the epileptic fit, indicate the need for an extensive series of examinations of a large number of patients. The technic is

2. Williamson, N. E.: A Chair for Spinal Puncture, J. A. M. A. **74**:602 (Feb. 28) 1920.

very simple but delicate. If the fluid stands a short while, the reaction changes quickly toward the alkaline side. Therefore, the hydrogen ion concentration was determined immediately on finishing the tap. Three cubic centimeters of spinal fluid was mixed with 1 c.c. of 0.2 per cent. aqueous solution of the indicator and the color thus produced in the fluid matched with a series of standard solutions until a satisfactory reading was secured. The average value obtained was a p_H of about 7.75, and in most cases the variations from this average were slight. In about 10 per cent. of the cases readings ranged as high as 8.1, which would indicate a slightly abnormal alkalinity of the fluid. However, we believe that these results are comparable to similar findings by other authors in normal persons, so that the results of the tests reported here do not tend to prove any particular theory.

PROTEIN CONTENT

Little is to be said about the albumin and globulin findings in these cases. One fluid with 350 cells, nearly all of the lymphocytic type, showed the presence of globulin. A few other fluids gave a slightly positive Ross-Jones reaction, but in 90 per cent. of those examined for these proteins the result was negative; i. e., globulin was not detected by the use of a saturated solution of ammonium sulphate, and the amount of albumin was not higher than 0.02 per cent. In none of the fluids did the albumin content rise above 0.03 per cent. These findings fail to confirm the opinion that idiopathic epilepsy is frequently accompanied by a moderate lymphocytosis. Not less than 78 per cent. of the fluids examined had fewer than 5 cells per cubic millimeter.

Levinson's [3] test with mercuric chlorid and sulphosalicylic acid was performed on all fluids on which albumin tests were done. This interesting test—the physiologic basis of which is unknown—could not be satisfactorily carried out, since the total amount of albumin present in the fluids was too scant to permit a convincing comparison.

PERMEABILITY OF MENINGES

In regard to the permeability of the meninges to various substances, most observers concede that under normal conditions few substances pass from the blood into the cerebrospinal fluid. The epithelium of the choroid plexus presents an impenetrable barrier to the majority of substances, and thus protects the delicate nervous structures from harm. Toxins do not pass. For example, tetanus toxin injected subcutaneously does not appear in the fluid. The specific agglutinin found

3. Levinson, Abraham: Cerebrospinal Fluid, St. Louis, C. V. Mosby Company, 1919.

in typhoid fever is also absent from the spinal fluid. However, the exclusiveness of the hemato-encephalic barrier is not quite complete. Alcohol and chloroform are allowed ready passage, and hexamethylentetramin administered internally can be recovered from the fluid.

In inflammatory conditions, the resistance of the meninges is decreased, and substances which cannot be detected in the spinal fluid under normal conditions may then be found. In ten epileptics of this series, the permeability to potassium iodid, and in five others the permeability to sodium nitrate, was tested. Both reagents could be found in the spinal fluid only under pathologic conditions. The technic was as follows: 16 grains (1 gm.) of potassium iodid in a 10 per cent. solution was injected intramuscularly twelve hours before the puncture; the fluid was then examined for the presence of iodid with the nitric acid and chloroform test. To test the permeability of the meninges to sodium nitrate, 2 gm. of sodium nitrate in a 10 per cent. aqueous solution was given by mouth three hours before the tap. The spinal fluid then was examined for nitrate by means of the ferrous sulphate test.

In the first case in which potassium iodid was used, a solution of greater concentration than 10 per cent. was injected; a local gangrene developed which healed slowly. In no case tested was the chemical administered discovered in the spinal fluid. The apparently normal permeability of these test cases militates against the theory that toxins of unknown origin, passing from the blood stream into the cerebrospinal fluid, cause the epileptic seizure.

PRESENCE OF CHOLIN

Special attention was given to the question whether the spinal fluid in epileptic patients contains waste products. The fact that a number of patients show macroscopic and microscopic changes in the structure of the brain stimulated a search for these substances in the spinal fluid. Like other authors, we used the presence of cholin in the spinal fluid as an indicator of these tissue dissolution processes. In this connection, it should be remembered that one is justified only in inferring that a positive reaction indicates a pathologic process, and that a negative result does not exclude the possibility of pathologic change in the tissues.

The method used was that of Rosenheim. Two cubic centimeters of spinal fluid was extracted in 95 per cent. alcohol. After evaporation of the alcohol, Rosenheim's reagent, an aqueous solution containg 2 per cent. iodin and 6 per cent. potassium iodid, was applied to the residue. This was done on a watch glass under the microscope. In positive cases, crystals of the shape of hemin crystals and consisting of cholin periodid were seen. In three of the forty-four cases tested for cholin, the reaction was positive. These results confirm the previous

observations of Donath,[4] who reported the occasional presence of cholin in the spinal fluid of epileptic patients. The low percentage of positive findings in comparison with the relatively much higher percentage of brain changes discovered at necropsy indicates that this test it not practical for diagnostic purposes.

NINHYDRIN REACTION

The literature contains observations from which it is claimed that the proteolytic effect of the individual's own serum on his brain tissue causes epileptic convulsions. From this point of view, one might expect that the products of such destructive proteolytic processes would be present in the fluid and could perhaps be detected by suitable reactions. In this study, therefore, the cerebrospinal fluids of twenty-five patients were examined for the presence of amin substances by means of Abderhalden's ninhydrin reaction. This sensitive test is simple: 1 c.c. of spinal fluid is mixed with 0.1 c.c. of a 1 per cent. ninhydrin solution in a test tube and the mixture is then carefully heated to the boiling point and held there for one minute. Change of the colorless fluid to a bluish violet tint indicates the presence of amin bodies. Of the fluids tested 28 per cent. gave positive results. Only 20 per cent. were negative. All others showed changes in color and developed a reddish brown tint of varying intensity. The relatively few examinations reported here are insufficient to warrant generalization on this point.

CHLORID CONTENT

Little can be said of quantitative findings in the chlorids. The simple method of Mohr, by which the test can be performed in a few minutes, proved satisfactory. Potassium chromate was used as an indicator and allowed exact final readings. The amount of chlorids in nearly all of these cases proved to be constant. The average value obtained was 0.7 per cent., and only few variations either above or below this level were observed. This is not astonishing if one considers the constancy of the albumin values previously noted, since the mutual interdependence of these two factors is widely recognized.

UREA AND SUGAR CONTENT

The amount of urea and sugar in the spinal fluid was measured, and parallel blood determinations were carried on at the same time. For the determination of urea the method of Van Slyke-Cullen was used. A comparison of the blood and spinal fluid findings revealed the fact that a close relationship exists between the results obtained in the two

4. Donath: Das Vorkommen und die Bedeutung des Cholins in der Zerebrospinalflüssigkeit bei Epilepsie u. organischen Erkrankungen des Nervensystems, Ztschr. f. physiol. Chem. **39**:526, 1903.

instances. The average values were 26 mg. of urea in 100 c.c. of spinal fluid and 29 mg. in 100 c.c. of blood. The readings of the authors ranged from 14 mg. to 45 mg. and fell within the limits given for normal persons. In 76 per cent. the blood urea was higher than that of the spinal fluid; in 5.9 per cent. the content was practically the same in the two, and in 17.6 per cent. the amount present was higher in the fluid than in the blood.

The sugar content of the spinal fluid has been much discussed for a number of years. It is now generally recognized that in normal persons each individual exhibits a fairly constant level which is subject only to small temporary changes. The normal value given varies with different writers and seems to depend on the method used, but it is placed by most authors between 50 and 80 mg. per 100 c.c. of spinal fluid. This very wide range for normal values naturally entails difficulties in evalu-

Blood and Spinal Fluid Sugar in Ten Cases

	Blood Sugar Mg. per 100 c.c.	Spinal Fluid Sugar Mg. per 100 cc.
H. W.	62	58
I. R.	87	81
D. B.	108	44
G. F.	94	78
E. C.	81	64
C. B.	94	80
M. D.	101	84
M. W.	84	49
S. G.	102	86
J. O.	100	81

ating the results obtained in this study. The colorimetric method of Folin-Wu was used, but it was necessary to modify the original method of these writers because of the small amount of albumin present in the spinal fluid. The amount of sulphuric acid used in the original method produces an excess of acidity in the solution to be tested, which impedes the reduction of the copper tartrate by the sugar. Therefore, the amount of sulphuric acid solution was decreased until it was learned by comparative examinations that the final reading was not appreciably influenced by the complete omission of the preliminary precipitation of the albumin with sulphuric acid and sodium tungstate solution. Thereafter, the spinal fluid was treated like an albumin-free sugar solution. In comparing the spinal fluid and blood findings of the same person, a lower amount of sugar in the fluid than in the blood was found in every instance. Ten cases, arbitrarily selected from the whole series, show the picture given in the accompanying table.

In reference to the findings of other authors in normal persons, we consider our values low but normal. Furthermore, it may be remarked that there is no general consensus of opinion regarding normal blood sugar values. The observations of different authors vary from 60 to 110 mg. per hundred cubic centimeters. In only one case in this study was a distinct dependence of the spinal fluid value on the blood value observed. In this case both blood and spinal fluid values were much increased, the former reaching a level of 146 and the latter 101. In general, however, no such correlation of the two values was observed, and a relatively high or low finding in the blood was not usually accompanied by a correspondingly high or low spinal fluid value. One hour after the introduction of sugar into the system, distinct hyperglycemia can be found in normal persons. There is, however, no accompanying hyperglycorrhachia or increase in spinal fluid sugar, at or after that time. This observation indicates that the sugar usually does not pass into the fluid from the blood like a transudate.

The observations reported here are in accord with the findings of Wittgenstein,[5] who notes the independence of the physiologic glycemia from the spinal fluid sugar in normal persons, but finds a distinct dependence in cases of hyperglycemia. The absolute decrease of the sugar in all kinds of meningitis, and the increased amount present in cases of encephalitis is so well known that it requires no discussion here.

After finishing the examinations reported, we found in the literature accounts of an observation, which, if true, is of great theoretical importance. Wittgenstein finds that patients with idiopathic epilepsy have a higher amount of sugar shortly after the seizure than during the interparoxysmal periods. As we did not perform comparative studies before and after the epileptic attack, we are not able to discuss this question. If confirmed, this observation may be used as a point in the differential diagnosis between hysterical and true epileptic convulsions.

Without attempting to draw further conclusions, it may be said that, irrespective of the type of epilepsy from which the fluid was taken, the sugar value was usually from 50 to 70 per cent. of the corresponding blood sugar, and that both generally had a low level. Further investigation of the subject should provide more complete and satisfactory information about blood and spinal fluid values, before, after and, if possible, during the epileptic convulsion. The dependence of the blood sugar level on vagal and sympathetic irritation, the topographic relations of the sugar center to the lower cerebral centers and the ventricular system, and the now well substantiated observation that a sudden drop in

5. Wittgenstein, A.: Klinische Bewertung des Zuckergehaltes im Liquor cerebrospinalis, Deutsch. med.Wchnschr. **49**:246 (Feb. 23) 1923.

the blood sugar value after insulin administration is followed by epileptiform convulsions, are all facts that ought to stimulate more interest in this inviting aspect of the problem.

COLLOIDAL REACTIONS

In the present study, we found opportunity in forty-seven cases to perform three parallel colloidal tests at the same time; namely, the reactions with colloidal gold, mastic and benzoin solutions. The colloidal reactions find much favor with many workers, but are regarded with distrust by many others. This aversion is perhaps due to the difficulty encountered in technic. Many modifications have been proposed, but the final difficulty proves to be the same in practically all. Some interesting experiences were met with in the preparation of the colloidal gold solution. The original Lange method, which had formerly been used with excellent results by one of us (P. L.), suddenly gave very unsatisfactory preparations when one of the common laboratory manuals was used as a guide for preparing the stock solutions needed. Three books were consulted; all described the same method, and all were wrong in their directions. One stock solution on which the efficiency of the colloidal gold chiefly depends is the formaldehyd solution. Wood and Vogel [6] recommend the use of 0.83 c.c. of a 2.5 per cent. solution of 37 per cent. formaldehyd solution for the preparation of 1 liter of the standard solution. Instead of a satisfactory gold solution, this method gave a bluish inklike stain. Then the formula of Lewinson was adopted and 5 c.c. of a 1 per cent. "formaldehyd solution" was used with an equally poor result. Boyd advocates the use of 10 c.c. of a "1 per cent. formalin solution." This method, however, also led to failure to secure a usable solution. After many unsuccessful experiments, it was decided that the formulas in the books cited are impracticable, as the terms "formalin" and "formaldehyd" are confused. The content of the ordinary solution of formaldehyd, U. S. P., contains about 40 per cent. formaldehyd. This solution should be used in the amount of 0.83 c.c.; otherwise, the formula of Wood and Vogel may be followed. By this method most of the difficulties of preparing satisfactory gold solutions were met.

Another point must also be considered. Solutions perfect in color vary greatly in their sensitivity. This variation is due to the acidity of the gold chlorid and of the stock solution of formaldehyd. An acid colloidal gold solution is too sensitive, while an alkaline one is not sensitive enough. If a solution prepared according to the usual method

6. Wood, F. C.; Vogel, K. M., and Famulener, L. W.: Laboratory Technique. The Methods Employed at St. Luke's Hospital, New York, James T. Dougherty, 1917.

proves too sensitive when tested with normal spinal fluid or with saline solutions of varying concentrations, it is possible to desensitize it by adding from 3 to 10 c.c. of a 2 per cent. potassium carbonate solution to 1,000 c.c. of the final preparation. The glassware used in the process must be absolutely clean. Before use, the glassware employed in this work went through a strong mixture of hydrochloric and sulphuric acids, and then was rinsed several times in distilled water and dried in the sterilizer. Good solutions were always obtained with only once distilled water. Mellanby and Anwyl-Davies,[7] and Hayden,[8] recently proposed a simple method of preparation, which gave us satisfactory results and made it possible to prepare a good solution in less than half an hour. To overcome the acidity of the gold chlorid solution, Hayden titrates the gold chlorid against potassium hydroxid. He then neutralizes the gold chlorid solution. His technic has a further advantage in that formaldehyd is not used. To 1,000 c.c. of distilled water, he adds 10 c.c. of a 1 per cent. potassium oxalate solution; the mixture is then heated to the boiling point. While boiling, 10 c.c. of the neutralized 1 per cent. aqueous gold chlorid solution is run in drop by drop. A clear solution of colloidal gold is thus quickly obtained.

The preparation of the colloidal mastic solution is as simple as that of the colloidal gold solution. However, the mastic gum on the market is very impure and gave unsatisfactory results. This objection was overcome by carefully separating the dirt particles from the gum with a pair of forceps. The methods of Emanuel [9] and Cutting [10] were used with apparently equal success.

In preparing the colloidal benzoin solution, the original French method was used. This test, discovered only a few years ago, is not as much in use as its value merits. The technic is simple. Ten grams of purified benzoin gum is added to 100 c.c. of absolute alcohol and the mixture kept in a bottle and shaken at intervals for forty-eight hours. The supernatant fluid, which is then poured off, constitutes the stock solution. The saline standard solution contains 0.1 gm. sodium chlorid in 1,000 c.c. of distilled water. To prepare the solution for a test: 20 c.c. of distilled water is placed in a clean flask; the water is then heated to 35 C., and 0.3 c.c. of the stock benzoin solution is added. This at once gives an opalescent colloidal solution of benzoin gum. Sixteen tubes

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7. Mellanby, J., and Anwyl-Davies, T.: Brit. J. Exper. Path. **4**:132 (June) 1923.

8. Hayden: A Note on the Preparation of Colloidal Gold Solution by the Mellanby Anwyl-Davies Technic, J. Lab. & Clin. Med. **10**:310 (Jan.) 1925.

9. Emanuel: Eine neue Reaktion zur Untersuchung des Liquor Cerebrospinalis, Berl. klin. Wchnschr. **52**:792, 1915.

10. Cutting, J. A.: A New Mastic Test for the Spinal Fluid, J. A. M. A. **68**:1810 (June 16) 1917.

are used for the test. Into the first tube is introduced 0.5 c.c., in the second 0.75 c.c. and in the third tube 1.5 c.c. of the standard saline solution. In each following tube 1 c.c. of the saline solution is used. To the first tube 0.5 c.c. of spinal fluid is added, to the second 0.25 and to the third 0.5 c.c. As in other spinal fluid colloidal tests, 1 c.c. of the mixture in the third tube is transferred to the fourth tube and, after mixing, 1 c.c. of the mixture is transferred into the tube immediately following and so on. Then 1 c.c. of the colloidal solution is added to all sixteen tubes. At room temperature the precipitation is usually completed after from six to twelve hours. With normal spinal fluid complete precipitation occurs in Tubes 7 or 8, whereas, pathologic fluids show precipitation in Tubes 1 to 5 and 7 to 10. The method described produced satisfactory solutions. However, the sensitivity of the solutions was not always the same. Even after a solution had been prepared and in use for some time, it was sometimes found to show changes in stability.

All three tests are of much practical worth if used with the necessary precaution. A spinal fluid may precipitate different colloidal solutions of the same kind in a varying degree. The degree of precipitation with any given solution may differ with the age of the solution, changing in some unknown way as the solution becomes older or "ripens," but the degree of precipitation is less significant than the type of the curve. In other words, the test should be regarded as qualitative rather than quantitative.

An astonishingly high percentage of cases gave a pathologic curve. Not less than 91.5 per cent. reacted to colloidal gold, 66.0 per cent. gave a reaction to colloidal mastic, and 83.0 per cent. reacted to colloidal benzoin. In only 10.6 per cent. of the cases examined were the reactions positive with both gold and mastic alone; 25.5 per cent. were positive to both gold and benzoin alone, and 49.0 per cent. were positive with all three reactions. The type of the gold curve was that of cerebrospinal syphilis in 97.0 per cent. of the gold curves; the precipitation started slowly in the second or third tube, reached its maximum depth in the fourth and fifth tubes and returned to normal in the second or third tube thereafter. The curve resembled that of general paralysis in 3.0 per cent.

Varying results were obtained with the benzoin test. In 17.0 per cent. of the cases, no reaction at all occurred. In 7.3 per cent., a slight precipitation appeared in the first three or four tubes. In 31.3 per cent, reactions were noted in Tubes 6 to 8; in 12.6 per cent., isolated and sporadic precipitation was seen in Tubes 8 to 10. In 43.9 per cent. of the cases a wavelike curve, with precipitation in several of the first tubes, no precipitation in the middle tubes of the set-up and a second precipitation in Tubes 6 to 10 was observed. In only one case was

there a precipitation in Tubes 1 to 13. This was a case in which a marked increase in albumin, globulin and cell count was noted following an injection of sodium phenobarbital twenty-four hours previous to the tap.

In one case with a negative gold reaction, the clinical picture presented may have been due to hysterical convulsions. The other cases referred to are all epilepsy of the unclassified type. The results obtained suggest the presence of some colloid-precipitating substance in the spinal fluids of a high percentage of these patients. The nature of this substance is unknown since there was no accompanying increase in the globulin content of the fluid.

INTRASPINAL INJECTION OF SODIUM PHENOBARBITAL

In a few cases the writers had the opportunity to study the effect on the spinal fluid of the injection of sodium phenobarbital. As indicated in another paper, the cell count rose very high, and even reached 6,000 when toxic doses were given. One case thus examined, with a normal picture except for the colloidal curve, at the first tap showed a meningitic gold curve with complete precipitation in Tubes 4 to 8, an increase of from 0 to 2,000 cells in one day, and a decrease in sugar content from 70 to 54 mg. per hundred cubic centimeters.

REACTION TO PUNCTURE

The reaction of these patients to the spinal tap was about the same as that of so-called normal persons. The injection of sodium phenobarbital after the puncture makes it impossible to determine exactly what were the reactions of the patients to the tap alone. However, it can be said that the amount of spinal fluid taken out had no influence on the severity of the symptoms. Patients from whom only a few drops of fluid were obtained would sometimes react more severely than those from whom 30 c.c. had been withdrawn.

SUMMARY

The purpose of this investigation was to determine whether the spinal fluid of epileptic patients exhibits any abnormalities. As far as the methods of investigation at our disposal permit a response, the answer must be largely negative. The conclusions drawn from the results obtained in this investigation are as follows:

1. Spinal pressure ranged from 6 to 38 mm. of mercury and was usually found at the upper borderline of the normal.

2. The pressure depended greatly on external influences, and rose in a few cases more than 100 per cent. when the patients were coughing.

3. In a few punctures made during severe seizures the pressure rose very high; in mild attacks it was not generally influenced.

4. The p_H varied little and was about the same as that of the spinal fluid of normal persons.

5. The number of cells per cubic millimeter was low; the cells found were chiefly of the small lymphocyte type.

6. The albumin content was within the normal range.

7. Globulin was absent, except in a few cases in which a faint trace was found.

8. The amount of chlorids was constant.

9. The content of urea varied, but the spinal fluid level was about the same as that of the blood.

10. The absolute sugar values found were low in both blood and spinal fluid. In every instance the content of sugar in the fluid was lower than that of the blood. These values are apparently independent of each other. One case of hyperglycemia, however, had a parallel hyperglycorrhachia.

11. The ninhydrin reaction was positive in a number of cases in which no abnormalities were found except in the colloidal curve.

12. Permeability of the meninges to potassium iodid and sodium nitrate was negative in the cases tested.

13. An unusually high percentage of positive reactions was encountered with colloidal tests.

14. The gold curve was that of the cerebrospinal syphilis type.

15. The colloidal benzoin curve varied in character.

16. No observations as to special findings in different types of epilepsy were attempted.

XANTHOCHROMIA IN EPIDEMIC ENCEPHALITIS

REPORT OF THREE CASES *

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In the literature on epidemic encephalitis there is little definite information to be found concerning the frequency of the occurrence of xanthochromic spinal fluid. In the investigation of the Association for Research in Nervous and Mental Diseases [1] it is reported as extremely rare. Scully quotes Leschke [2] as collecting 310 cases of yellow spinal fluid, of which two occurred in epidemic encephalitis while in the 339 cases that he himself collected from the literature none occurred in that disease.

In the year from Dec. 31, 1923, to Dec. 31, 1924, the spinal fluid of 1,279 patients was examined at the Boston Psychopathic Hospital; six cases showed xanthrochromia. Three of these occurred in cases of epidemic encephalitis. During that period thirty-two patients with epidemic encephalitis were admitted to the hospital, and thus for that year 9.38 per cent. of the cases of epidemic encephalitis showed xanthochromic spinal fluid. Because of the comparative frequency of this finding, it was thought to be of interest to report these cases.

REPORT OF CASES

CASE 1.—*History.*—Mr. E. R. P., aged 42, white, was admitted Dec. 28, 1923, and discharged April 19, 1924, unimproved. His mother died at the age of 76 of senile dementia. He had always been healthy until three weeks before admission, when he developed a severe boil on his neck. He was given four injections of a stock vaccine by his family physician, the last one on Dec. 25, 1923. For two weeks previous to admission he had not been sleeping well. On December 27 he was a little overactive, and at his office in the evening he became excited, violent and irritable, so that he had to be brought to the hospital by the police.

Examination.—On admission, he had a furuncle on the back of the neck and a slight pharyngitis. His temperature (rectal) was 101.6 F., pulse 108, respiration 22. The white blood count was 10,800. Urinalysis revealed: a specific gravity of 1.030, acid reaction, albumin test negative, sugar test ++, bile test negative, acetone test ±, diacetic acid test negative, sediment, amorphous urates. On the next day, however, urinalysis was negative. Complete examination was impossible on account of the patient's behavior, but his pupils reacted well to light and in accommodation; there was no gross cranial nerve palsy; the

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* From the clinical service of the Boston Psychopathic Hospital.

1. Acute Epidemic Encephalitis, an Investigation of the Association for Research in Nervous and Mental Diseases, 1921.

2. Leschke, E., quoted by Scully, Francis J.: Yellow Spinal Fluid, Its Origin and Significance, Arch. Neurol. & Psychiat. **10**:83 (July) 1923.

knee reflexes were equal and active, there was no disturbance in gait or speech. Mental status showed marked overproductivity. He seemed to be out of contact with the environment and was incoherent, with slight flight of ideas, occasionally showing distractibility and rhyming. He was elated at times; at other times, anxious and perplexed. Except for the fact that he knew he was at a hospital, he was disoriented. His memory and grasp of general information could not be tested and he appeared to have no insight.

Course of Illness.—On Jan. 1, 1924, choreic and athetoid-like movements were noted. On January 6, the patient developed an external strabismus of the left eye. On the next day there was a transient strabismus of the right eye. Lumbar puncture on January 7 revealed clear, colorless fluid, under normal pressure, albumin ++++, globulin ++++. The colloidal gold curve was negative. The spinal fluid sugar content was 0.208 per cent.; the next day it was 0.139 per cent. (proteins not precipitated). Unfortunately, a cell count was not made on this fluid. On January 10, a second lumbar puncture was performed; a clear yellow fluid was obtained, under normal or slightly increased pressure. Albumin and globulin tests were both ++++. The colloidal gold curve was 0005540000. The cell count showed 7 cells per cubic millimeter, all small lymphocytes, and many red blood cells. On the next day, January 11, another lumbar puncture showed a similar yellow fluid with globulin and albumin ++++, a colloidal gold curve 0001111110, a cell count of 4 per cubic millimeter, two small and two large lymphocytes. Neither this nor the previous specimen of spinal fluid coagulated. On January 10 the patient was seen in consultation by Dr. Horrax, who regarded the case as one of epidemic encephalitis. By January 12, the strabismus had practically disappeared. On January 14, i. e., three days after the previous spinal puncture, another lumbar puncture showed clear, colorless fluid, under normal pressure, 3 cells per cubic millimeter, consisting of 2 small and 1 large lymphocyte. The albumin and globulin tests and the colloidal gold curve were negative. On January 19 another spinal fluid specimen was obtained. It was under normal pressure, clear and colorless; the albumin test was ++, the globulin test + and the cell count 4 per cubic millimeter, all small lymphocytes. The colloidal gold curve was negative. Five days later, on January 24, another lumbar puncture showed a clear colorless fluid under normal pressure, 2 cells per cubic millimeter, both small lymphocytes, some red blood cells, albumin and globulin tests both ++++ and a colloidal gold curve of 0122220000. The final lumbar puncture was performed on March 1, 1924, and showed a clear colorless fluid, under normal pressure, with 2 cells (one small lymphocyte, one endothelial cell) per cubic millimeter. The albumin test was +, the globulin test negative and the colloidal gold curve ±±± 1100000.

Throughout the patient's three and one half months' stay in the hospital his condition remained essentially the same, i. e., he showed overactivity, incoherence and loss of contact with the environment. Two or three times, however, he showed some change in the direction of a more typical manic reaction, with distractibility, flight of ideas, rhyming and punning. For a considerable period of time his temperature was slightly elevated. It rose to 103 F. (rectal) on January 7 and then remained fairly steady at 101 F. until February, when it became normal. Toward the end of February it rose gradually to 102, falling within a few days again. It continued normal until discharge, except for a sudden rise to 101 on April 17. The white blood count after the initial count of 10,000, varied from 12,200 to 18,900. Blood culture and Widal tests were negative. On Jan. 8, 1924 (one day following the first lumbar puncture), the

nonprotein nitrogen content of the blood was 41.4 mg. per hundred cubic centimeters, and the sugar content was 0.12 per cent. Cultures and smears of the spinal fluid were negative. Wassermann tests of the blood and spinal fluid were negative.

The patient was discharged to a private hospital on April 19, 1924, and is there at present (July, 1925). He is reported there to have at first shown a fairly typical manic picture, sometimes, however, with confusion, auditory hallucinations and extreme insomnia. He gradually quieted down until September, 1924, when he became more active and exhilarated. Since then there has been a gradual abatement in his condition with more frequent fairly lucid intervals since March, 1925. His physical and neurologic examinations have remained essentially negative.

CASE 2.—Miss M. M., aged 40, a school teacher, was admitted to the hospital on March 20, 1924, and died, April 3, 1924. In January, 1921, the patient's appendix was removed. She was then said to have chronic interstitial nephritis, and her people were informed that she might not live more than three years. In January, 1924, she developed a number of sores over one eyebrow and on the scalp of the same side, preceded by a short period of pain and itching. Two or three days later she developed a considerable swelling on both sides of the neck, resembling mumps. She remained in bed for a few days, and was unable to return to work for five or six weeks. A week before admission she complained of pain in the region where the sores had occurred. Several days later, on March 18, 1924, she was heard moaning in her room and did not respond to inquiries at the door. On March 19, she was semistuporous and confused, and she remained in that condition until admission.

Examination.—On admission, examination revealed a large, middle-aged woman, drowsy and looking ill. There was a moderate exophthalmos. There were numerous deep, pitted scars about 1 cm. in diameter over the left eyebrow, arranged in a triangular form. The aortic second sound was accentuated; the blood pressure was: systolic 220, diastolic 150. There was tenderness to deep pressure in the right upper quadrant. Neurologic examination showed a bilateral ptosis of the upper lids and a slight horizontal nystagmus to the left. The pupils were contracted and irregular, fixed to light and reacted fairly well in accommodation. Her deep reflexes were equal and active. There was some generalized weakness, but no localized paresis or paralysis. She was generally hyperesthetic, but no other sensory changes were found. The plantar reflexes were normal. There were no tremors or incoordination. Her temperature was 99.3 F. (rectal), pulse 95 and respiration 22. The white blood count was 34,800.

Mental examination revealed essentially the picture of a delirium with confusion, semistupor and disorientation.

Course of Illness.—On March 22, the patient was seen by Dr. Campbell. There was then noted an external strabismus of the left eye. This cleared up within two days.

A lumbar puncture was performed on March 23, and xanthochromic fluid was obtained. There were 640 cells per cubic millimeter, consisting of 90 per cent. polymorphonuclears, 7 per cent. small lymphocytes, 2 per cent. large lymphocytes and 1 per cent. endothelial cells. Microscopically, the fluid was filled with red blood cells but not enough, allowing for the leukocytosis, to account for the increased white count. Albumin and globulin were both $+++$. It did not coagulate, nor did its color change on standing. The spinal fluid sugar was 0.0633 per cent. The colloidal gold curve was 01132 ± 0000. A culture of the spinal fluid was negative. Two subsequent lumbar punctures were performed,

one on March 26, when the fluid was clear and colorless but microscopically showed frequent red blood cells, a white count of 1 small lymphocyte per cubic millimeter and a colloidal gold curve of 0045310000. Another was performed on April 1, when it was grossly bloody, with 6 white blood cells per cubic millimeter (4 small lymphocytes, 1 polymorphonuclear and 1 endothelial cell) and a colloidal gold curve of 112220000. The patient's temperature, which was normal on admission, rose within a few days to 104 F. (rectal) and gradually subsided to 102, where it remained until a few days before death, gradually rising to 104. The pulse rate hovered about 120, rising to 140 during the last two days. The respirations remained at 22 per minute until April 1 when they were 45, rising to 55 before death. The white blood count varied from 30,000 to 40,000. The Wassermann tests of the blood and spinal fluid were negative. The urine on several occasions showed a specific gravity of 1.016 to 1.018, alkaline reaction, a slight trace of albumin, no sugar and an occasional fine granular cast. The nonprotein nitrogen of the blood on March 22 was 90 mg. per hundred centimeters, but within a week it fell to 33.3 mg. The blood sugar was 0.172 per cent.

On March 26 the fundi were examined by Dr. Goodall, who made a diagnosis of probable albuminuric retinitis with many hemorrhages. On March 27 the patient developed a stiff neck, and no arm reflexes could be obtained except in the left biceps and the right wrist reflex. The knee reflexes were present but difficult to elicit. There was no paralysis, and the pupillary findings were unchanged. On April 2, there was retraction of the head with a definite Kernig sign, the deep reflexes were a little more active on the left, with a questionable left Babinski sign. The patient's mental status was unchanged, except that she became more difficult to arouse. She finally became comatose, and died on April 3, at 11 p. m.

Necropsy.—Postmortem examination revealed a hypostatic congestion of the lungs, acute dilatation of the right auricle with cardiac hypertrophy, passive congestion of the spleen and liver, acute cystitis, moderate generalized arteriosclerosis, a cystic left kidney, chronic vascular nephritis, an old healed tuberculous lesion at the apex of the right lung and a slight chronic leptomeningitis. There were two pial hemorrhages, one over the left parietal region, and the other over the left superior surface of the cerebellum. The base of the brain was diffusely reddened, and there were small hemorrhages under the olfactory tract. There was a blood clot, probably not more than twenty-four hours old, filling both lateral and the third ventricles, with the fourth ventricle partly involved. In the cervical region of the cord there was a small blood clot between the pia and dura. Microscopically, there were perivascular exudates in the region of the midbrain, characteristic of epidemic encephalitis.

CASE 3.—*History.*—Mr. M. W., aged 43, admitted to the hospital on Dec. 15, 1924, was discharged on Dec. 23, 1924, unimproved.

The family and personal history were unimportant. Two weeks before admission the patient wept, saying he would go crazy from worry over his business which had been going badly for two or three months. He vomited twice and was very pale. There was no history of trauma. On the next morning he complained of headache above his nose and eyes and pains all over his body. His private physician thought he had influenza. He remained in bed until December 10, when he returned to his business, but he soon came back feeling weak and went back to bed. On December 11 he went to work, but complained of a steady, severe headache. On December 12 he woke up moaning and crying that his head ached. After being given 15 grains (0.97 gm.) of acetylsalicylic

acid he slept nearly all day, wetting the bed once during that time. At night he began talking aimlessly about his father and mother and acted as though his business were going on about him. This continued until his admission to the hospital on December 15.

Examination.—Examination on admission revealed a well developed, middle-aged white man with a slightly reddened pharynx, some pyorrhea and moderate emphysema. The blood pressure was: systolic 115, diastolic 80. Neurologically he showed a bilateral partial ptosis of the upper eyelids, a questionable bilateral external rectus weakness, poor convergence, pupils somewhat myotic and sluggish both to light and in accommodation, with a washed-out facies, generally diminished but equal deep reflexes, and suspicious but not definite Babinski and Chaddock signs on the right. There was a slight tremor of the outstretched fingers and moderate generalized weakness, but no myoclonic or fibrillary twitchings. Although generally hypersensitive to deep pressure, pain, postural and tactile sensations were normal. There were no meningeal signs. The fundi were negative.

Mental status showed marked underactivity. Usually the patient was sleeping, slightly stuporous or apathetic. He was confused at times and in poor contact. He talked little, spoke in an indistinct mumbling tone, was coherent but circumstantial and occasionally irrelevant. He was depressed, weeping frequently. There were vague transitory delusions of persecution. His memory and grasp of general information were markedly disturbed. He had poor insight. His temperature was 98.3 F. (rectal) on admission, his pulse rate was 85, and his respirations were 20 a minute. His temperature fluctuated from 98.3 to 100.2 (rectal) throughout his stay. The white blood count was 7,800. Urinalysis was negative.

Course of Illness.—A lumbar puncture was performed on December 19. Clear, light yellowish fluid, under somewhat increased pressure was obtained. There were 78 cells per cubic millimeter, 58 small lymphocytes, 10 large lymphocytes, 5 polymorphonuclears and 5 endothelial cells. There was an occasional red blood cell. The globulin test was +. The total protein content was 75.2 mg. per hundred cubic centimeters; the sugar content was 0.072 per cent. The colloidal gold curve was negative. The fluid did not coagulate on standing. Wassermann tests of the blood and spinal fluid were negative.

Dr. Campbell who saw the patient on December 18 regarded him as probably having epidemic encephalitis. During his eight day stay at the hospital his condition remained the same, except that the bilateral ptosis had almost disappeared, and he was more alert than on admission. After leaving the hospital, he had a rather stormy convalescence but with a gradual subsidence of his confusion, and he is at present (July, 1925) apparently completely well.

COMMENT

It is doubtful whether the yellow spinal fluid in the second case should be ascribed to the epidemic encephalitic process, as it seems more likely to have been due to a concomitant renal and vascular disorder. The xanthochromia does not seem to be directly dependent on the severity of the meningeal process, judging by the cell count, which varied from normal up to 640 per cubic millimeter, and the absence of meningeal signs in two of the cases. In two of three cases there were considerable numbers of red cells in the spinal fluid. This would seem to put them

fairly definitely in the group due to hemorrhage rather than that due to a transudative process, and the necropsy findings in the second case would confirm this. It is noteworthy that in all three of these cases the mental symptoms overshadowed the physical ones from the start. This would seem to point to the conclusion that xanthochromia in epidemic encephalitis is more likely to be found in those cases in which the mental symptoms are especially prominent. The prognosis so far as immediate effects are concerned does not seem to be especially altered by the occurrence of xanthochromia, but it is still too early to form any opinion in regard to later manifestations.

DIFFICULT URINATION ASSOCIATED WITH INTRACRANIAL TUMORS OF THE POSTERIOR FOSSA

A PHYSIOLOGIC AND CLINICAL STUDY *

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Disturbances in the act of urination in the conscious, rational person are a frequent accompaniment of spinal cord disease, and in most instances are attributed to pathologic alterations in the lumbar and sacral regions involving the lower cord "center" for micturition. The retention of urine which accompanies upper spinal cord tumors suggests, however, that these urinary difficulties may be due to some interference with the passing of impulses from a higher center, and additional evidence in support of this view is obtained from a study of similar urinary disturbances associated with intracranial tumors located in the posterior fossa. In these cases there is no question of a lower cord lesion.

Normal micturition is said to be accomplished through the coordination of two complementary nerve-control mechanisms through the hypogastric nerves and the nervi erigentes.[1] The upper four lumbar nerves send white rami communicantes to the lateral chain of the sympathetic system and thence to the inferior mesenteric ganglion grouped around the inferior mesenteric artery. A new relay of axons from this collection of ganglion cells passes by way of two main trunks, the hypogastric nerves, to the hypogastric plexus at the base of the bladder, and thence to the bladder wall.

The nervi erigentes make no connection with the sympathetic system, but are derived from the second and third sacral nerves. The fibers in these nerves pass to a group of cells located in the hypogastric plexus and in the walls of the bladder, the axons of which terminate in the bladder wall.

Excitation of the fibers in the nervi erigentes results invariably in a strong contraction of the bladder wall, the detrusor urinae, and there is some evidence that such excitation also results in inhibitory impulses to the sphincter muscle at the base of the bladder. Stimulation of the hypogastric nerves varies in its effect depending on the animal under experimentation, but there is invariably a strong contraction of the

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1. Starling, E. H.: Principles of Human Physiology, London, J. & A. Churchill, 1912, p. 1289-1298. Fearnsides, E. G.: The Innervation of the Bladder and Urethra, Brain **40**:149-187 (Nov.) 1917.

muscle fibers at the base of the bladder, especially of the trigonum and of the sphincter trigoni, with some evidence that there results also an inhibitory effect on the detrusor urinae. These observations are interpreted as indicating that the retention of urine and the distention of the bladder are the results of a reflex dilatation of the bladder wall and of a reflex constriction of the sphincter excited through the hypogastric nerves, whereas the complete evacuation of the bladder is considered to be a function of the nervi erigentes, stimulation of which causes the bladder wall to contract and the sphincter to relax.

This phenomenon of crossed innervation in control of the physiologic functions of the body, as exemplified in micturition, was termed by Meltzer [2] "the law of contrary innervation," and by Sherrington [3] "the law of reciprocal innervation." It is a fundamental concept, indispensable in our understanding of all physiologic processes having to do with muscular contraction, whether voluntary or involuntary.

The bladder is provided not only with the nonstriped or true sphincter, innervated through the hypogastric nerves, but also with a striped or external sphincter, the compressor urethrae muscle. This muscle is supplied by the pudic nerve from the second, third and fourth sacral nerves. Under certain conditions, notably following prostatectomy, the sphincter action is said to be taken over by this compressor urethrae muscle.

The manner in which the processes of retention and evacuation of urine are modified and controlled by voluntary effort is still not clearly understood. In the words of Starling, "The reflex process of evacuation of urine may be set in motion by voluntary contraction of the abdominal muscles, by which pressure in the bladder is increased and the normal sphincter action overcome. It is probable, too, that the individual has a certain degree of voluntary control over the unstriated muscles of the bladder, and that the contraction of the muscular wall may be directly augmented by impulses proceeding from the cortex to the upper part of the lumbar cord."

That the functions of the bladder may be exercised quite independently of the higher centers is demonstrated in children in whom reflex involuntary micturition may be evoked by emotion, by irritation of pelvic organs or by strong sensory stimulation.

Further evidence of bladder activity independent of central control was obtained during the Great War by various workers, notably Head

2. Meltzer, S. J.: The Disturbance of the Law of Contrary Innervation as a Pathogenetic Factor in the Diseases of the Bile Ducts and the Gallbladder, Am. J. M. Sc. **153**:469-477 (April) 1917.

3. Sherrington, C. S.: The Integrative Action of the Nervous System, New York, Charles Scribner's Sons, 1906.

and Riddoch [4] and Thomson-Walker,[5] in their observations on wounded soldiers.

Immediately following complete division of the spinal cord in the cervical, thoracic and lumbar regions, all power of voluntary micturition was abolished. There was atony of the detrusor muscle, but the sphincter remained actively contracted. Unless repeated catheterization was performed, overflow and dribbling incontinence developed. In those instances in which damage to bladder musculature from overdistention was prevented by early and repeated catheterization, this period of retention gave place at first to occasional and fitful evacuation, and then to true automatic micturition occurring at periodic intervals. The patient was unable by any effort of will to initiate the reflex, or to inhibit the micturition. Under such circumstances the urine accumulated in the bladder up to a volume, different in each case, when it was automatically discharged. The point at which automatic discharge occurred was found by filling the bladder slowly through a glass buret, without pressure, the inflow being discontinued immediately when the fluid was seen to rise in the buret, as a result of bladder contraction. Filling the bladder with amounts varying from 200 to 500 c.c. provoked sufficient stimulus of the bladder wall to effect evacuation by contraction of the detrusor urinae and relaxation of the sphincter. A bladder which had never been unduly distended, or the site of infection, was capable of holding a larger amount of fluid before such evacuation occurred than the bladder whose musculature had suffered from repeated distention and prolonged cystitis. Under certain circumstances this act of automatic micturition failed to appear, particularly in those cases in which the bladder was allowed to become greatly distended, thus injuring the bladder musculature, or in which the injury was early followed by a cystitis, a pyelitis or large sloughing bed sores. The absence of automatic urination in the latter group of cases was attributed by Head to the loss of the tonic influence and reflex excitability of the cord through a toxic degeneration of that part of the cord lying below the site of injury. The stage of automatic micturition, once established, continued sometimes for months, usually yielding again to retention, dependent on a loss of reflex excitability through the same factors that occasionally prevented its appearance at all, namely, pyelitis, cystitis or sloughing bed sores.

During the stage of automatic activity, these authors described also the occurrence of an interesting phenomenon which they designated the "mass reflex." During the period of hyperexcitability of the cord,

4. Head, H., and Riddoch, G.: The Automatic Bladder in Injuries of the Spinal Cord, Brain **40**:188-263 (Nov.) 1917.

5. Walker, J. W. Thomson: The Bladder in Gunshot Injuries of the Spinal Cord, Lancet **1**:173-179 (Feb. 3) 1917.

reflexes could be evoked with great ease. Stimulation of the sole of the foot would excite not only those movements involved in the complicated act of withdrawing the leg, namely, flexion at the ankle, knee and hip; but also those reflex arcs in close proximity to the withdrawal arc. For example, the act of automatic micturition and automatic defecation could be set off by simply scratching the sole of the foot. The evidence from these war injuries indicates clearly that bladder activity may go on completely dissociated from cortical or central control.

Several attempts have been made to establish the presence of a cortical center of micturition. In 1901 Czyhlarz and Marburg [6] came to the conclusion, not justified by their cases, that "in unilateral lesions of the motor zone, presumably in the region of the hip center, lying between the arm and leg centers, there occurred retention of urine." They presented the following cases:

1. A tumor of the left lenticular nucleus associated with difficult delayed micturition. The head of the left optic thalamus was flattened, indicating that the lesion probably also distorted the midline structures.

2. A tumor of the pons associated with delayed and difficult micturition, paralysis of lower extremities and later incontinence.

3. A tubercle of the pons with paresis of the extremities, ataxia, retention of urine and later incontinence. Both pyramidal tracts were flattened.

Friedmann,[7] following observations on one person, located a cortical center for micturition in the motor area close to the arm center. The lesion was inflicted by a "Ziegelstein" which produced a depressed fracture of the skull in a circumscribed area. There was no loss of consciousness, but following an immediate operation for the removal and elevation of the bone fragments, the patient, a boy, aged 9 years, developed delayed and difficult urination which persisted for three weeks, and was then succeeded by a prolonged period of incontinence which was present only during the day and entirely absent at night. Gradual improvement occurred after a year. The boy was troubled during all this time with a pronounced "general nervousness." Furthermore, no direct evidence was obtained indicating that the lesion was as circumscribed as the author inferred from the presence of the visible depressed fracture. The extent of intracranial damage can under no circumstances be determined from the amount of external damage to the skull. In the face of these facts, these observations by Friedmann cannot be considered applicable in locating a cortical center of micturition.

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6. Von Czyhlarz and Marburg: Ueber cerebrale Blasenstörungen, Jahrb. f. Psychiat. u. Neurol. **20**:134, 1901; abstr. Neurol. Centralbl., 1901, p. 571.

7. Friedmann, M.: Zur Kenntnis der Zerebralen Blasenstörungen, München. med. Wchnschr. **50**:1591, 1903.

More definitely localizing evidence of a central control was obtained by numerous observers in the experimental laboratory. Greving,[8] in 1922, reviewed the work of Lichtenstern,[9] Karplus and Kreidl,[10] and Bechterew.[11]

Briefly, the evidence of these various authors points to a center for the control of bladder contraction located in the hypothalamus, and Greving suggests an even more exact localization in the front and medial parts of the subthalamus.

Lichtenstern's observations were very suggestive. Electrical stimulation of the hypothalamus produced sustained contraction of the entire bladder wall, which disappeared when warm water was poured over the exposed bladder, or when warm water was allowed to run slowly into the bladder. Division of the hypogastric nerves caused an accentuation of the contraction produced by stimulating the hypothalamus. On the other hand, division of the nervi erigentes abolished it entirely. Division of the "konus" of the spinal cord at the level of the third sacral nerve did not alter the contraction, whereas division at the level of the second sacral nerve abolished it. Following ablation of the right cerebrum, stimulation of the hypothalamus still resulted in contraction of the bladder. Ablation of both cerebral hemispheres caused an accentuation of the contraction.

These observations suggested that the seat of central control of the bladder lies in the hypothalamic region, more specifically in the subthalamus, from which impulses pass down the spinal cord and presumably reach the bladder through the nervi erigentes. Nerve fiber bundles from the subthalamus have been demonstrated passing to the pallidum and to the subthalamic region of the opposite side; and other fiber bundles lose themselves ventrally in the peduncles, whence they find their way down the cord.

Barrington has just published some important laboratory observations on micturition in the cat. In 1915, he[12] presented evidence that the coordinate act of micturition was not dependent on the integrity of a center in the lumbosacral cord, but on a more central control which

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8. Greving: Zur Anatomie, Physiologie, und Pathologie der Vegetativen Zentren im Zwischenhirn, Ztschr. f. d. ges. Anat.; Ergebn. d. Anat. u. Entwcklngsgesch. **24**:348-413, 1923.

9. Lichtenstern, R.: Ueber die Zentrale Blaseninnervation; ein Beitrag zur Physiologie des Zwischenhirnes, Wien klin. Wchnschr. **25**:1248-1249, 1912.

10. Karplus and Kreidl: Gehirn und Sympathicus, I bis IV, Mittheilung, Pflüger's Arch. f. d. ges. Physiol. **129**:138-144, 1909; **135**:401-416, 1910; **143**:109-127, 1918; **171**:192-200, 1918.

11. Bechterew: Die Functionen der Nervenzentren, Jena, 1909.

12. Barrington, F. J. F.: The Nervous Mechanism of Micturition, Quart. J. Exper. Physiol. **8**:33-71, 1915.

could be abolished by transection of the thoracic cord. Later he[13] reported that reflex micturition takes place normally in cats in the absence of the whole of the forebrain and anterior part of the midbrain, but is completely abolished by transection of the cervical cord or of the medulla as high as the apex of the calamus. He further demonstrated that the reflex contraction of the detrusor urinae from distension has both its efferent and afferent paths in the nervi erigentes, and that this reflex contraction is dependent on the continuity of the nerve paths of the spinal cord from the brain center controlling the motor tone of the bladder down to the origin of the sacral roots forming the nervi erigentes. This center he located approximately at the level of a plane through the posterior parts of the inferior colliculi dorsally and the middle of the pons ventrally. Recently he[14] has presented evidence that destruction of a small part of the hindbrain in the cat is followed by a permanent inability to empty the urinary bladder if the lesion is bilateral, but not if it is unilateral. Destruction of a small part of the midbrain is followed, when the lesion is bilateral, by a permanent loss of consciousness of wanting to micturate or defecate, but does not impair the performance in either of these functions. This evidence is not as definitely localizing as that of Greving, Lichtenstern, and others, and it seems probable that the center of micturition lies anterior to the region investigated by Barrington.

Little clinical evidence is available to substantiate the presence of this center of micturition, or to indicate its location. However, in the course of several years' experience in studying neurologic patients with presumed brain tumors, close questioning has brought to light suggestive information of an indirect nature in favor of such a central control. It was found that cerebellar tumors, particularly those located in the midline, or those which distort the midline structures by their great size, may interfere with the pathway leading from the center for bladder contraction to the sacral cord. This interference manifested itself either by a marked delay in the voluntary act of micturition lasting from one to ten minutes, or by a complete inability to void, in which case catheterization became necessary. This difficulty was not permanent, but occurred at intervals for varying periods of from one to seven days, after which urination again became normal. Occasionally it was followed by incontinence. It occurred in association with lesions similar to those presented by Czyhlarz and Marburg, and it is likely that the mechanism is the same in the two instances. The delayed micturition

13. Barrington, F. J. F.: The Relation of the Hindbrain to Micturition, Brain **44**:23-53 (April) 1921.

14. Barrington, F. J. F.: The Effect of Lesions of the Hind and Midbrain on Micturition in the Cat, Quart. J. Exper. Physiol. **15**:81-102 (March) 1925.

may be evidence of an interruption of impulses leading from the brain to the bladder, causing a paralysis of the detrusor, whereas the incontinence may be evidence of an irritation or excitation of the nerve bundles passing to the nervi erigentes, with contraction of the detrusor and relaxation of the sphincter.

In one instance (Case 8) the urinary difficulties were associated with an intractable constipation. Since the lower segment of the large bowel and rectum is innervated by the nervi erigentes, it is possible that interference with the outflow from these nerves was responsible both for this constipation and for the difficult urination. Stimulation of the nervi erigentes in animals causes a contraction of the muscular coats of the pelvic colon and rectum.

Intracranial tumors involving either cerebral hemisphere were unaccompanied by this symptom of delayed urination except in the irrational or unconscious individual. It is highly suggestive that when difficult urination is found in patients with other evidences of increased intracranial pressure, the lesion is probably located in the posterior fossa. It is quite possible that midbrain tumors would be accompanied by this symptom, although there are no instances available to warrant this assumption.

The following cases [15] are presented as illustrating the disturbances of micturition associated with posterior fossa tumors.

CASE 1.—I. T. J., an unmarried man, aged 22, entered the Johns Hopkins Hospital with a history of headaches, vomiting and dizziness, of fifteen months' duration. Diplopia, staggering gait and tinnitus in both ears developed, and following this a right-sided decompression had been performed in the month preceding his admission. There had been no sensory or motor disturbance aside from the unsteadiness. Since the beginning of his trouble there had been numerous short periods in which he experienced great difficulty in starting the flow of urine, alternating with normal micturition. There had been no dysuria. Examination revealed marked bilateral papilledema, a poorly sustained nystagmus on looking to right and left, hyperactive knee kicks and ankle clonus on the left. There were no sensory nor motor disturbances. The blood and spinal fluid Wassermann reactions were negative. A diagnosis of left cerebellar tumor was made.

At operation, a cyst of the vermis was disclosed which involved the left lobe of the cerebellum more than the right, and contained about an ounce of clear yellow fluid. A portion of the cyst wall was removed, which on microscopic section proved to be a glioma.

CASE 2.—G. P., a married woman, entered the Johns Hopkins Hospital complaining of headaches and blindness. The illness dated back five years, beginning with a loss of hearing on the left, accompanied by pain and tinnitus in the left ear and an awkwardness of the left hand, and followed several years later by

15. Case 1 was seen in the neurologic service of Dr. G. J. Heuer; cases 2 and 3 in the neurologic service of Dr. W. E. Dandy; cases 4, 5 and 6 in the neurologic service of Dr. Harvey Cushing, and cases 7 and 8 in the neurologic service of Dr. Elliott C. Cutler.

awkwardness in walking, particularly of the left leg. There then followed the usual train of symptoms accompanying the gradual development of a left pontile angle tumor: numbness and paralysis of the left side of the face, loss of taste on the left, difficulty in swallowing, intense generalized headaches, vomiting and gradual loss of vision which progressed to complete blindness.

In the three months prior to admission there had developed periods of complete retention requiring catheterization, alternating with periods of normal micturition. At the time of her admission to the hospital the patient was unable to void, and catheterization was necessary.

At operation a large left acoustic tumor about the size of a lemon was found, displacing to a very marked degree the left cerebellar lobe.

Case 3.—J. S., a boy, aged 9, was admitted to Johns Hopkins Hospital with a history of having developed, six weeks before admission, a stiff neck, headache, projectile vomiting, severe pains in the abdomen, convulsions and an internal strabismus. Two weeks after the onset of these symptoms there occurred a short period of difficulty in starting the flow of urine, followed by complete retention requiring catheterization for about a week.

Examination revealed a bilateral papilledema, dilatation of both pupils, a large hydrocephalic head with wide suture lines, paralysis of both external rectus muscles, great emaciation and weakness. The Wassermann reaction was negative. There were no paralyses nor sensory changes.

At operation a walnut-sized gliomatous cyst (microscopically confirmed) was disclosed in the upper part of the medulla, lying in the midline and extending down into the upper segment of the spinal cord.

Case 4.—J. R., a man, aged 29, entered the Peter Bent Brigham Hospital with symptoms of an advanced posterior fossa lesion; namely, tinnitus and increasing deafness in left ear, dysarthria, dysphagia, unsteadiness of gait, clumsiness of hands and failing vision. During the seven months before admission there had been considerable difficulty with urination. He frequently went eighteen hours without voiding, unattended by pain. At times when he felt like urinating, he was totally unable to start the stream. After a few minutes of rest he could void without difficulty.

Examination revealed a partial left ophthalmoplegia, hypesthesia of the left side of the face, weakness of the left jaw muscle, left facial weakness, diminution in taste on the left, complete left-sided deafness, deviation of the soft palate and tongue to the right, marked dysmetria, hypotonia and incoordination. There were no sensory disturbances.

A cerebellar exploration revealed a large left cerebellopontile tumor of the acusticus which was almost completely removed. There was complete retention of urine immediately after operation, requiring one catheterization, but there was no trouble thereafter.

Case 5.—F. P., a boy, aged 5, entered the Peter Bent Brigham Hospital with a history of headaches, vomiting, difficulty in walking and a clumsiness of the hands. During the six months preceding his admission there had been a number of occasions on which he had difficulty in starting micturition, but after some delay he was usually able to void. Occasionally he would give up the effort and this was followed by a soiling of the clothes or bed through incontinence. There was marked incoordination suggesting left cerebellar disease. There was a well marked bilateral papilledema. A ventriculogram indicated marked internal hydrocephalus.

A suboccipital exploration revealed a large firm tumor, located in the midline, probably a fibroglioma arising from the roof of the fourth ventricle.

CASE 6.—C. B., a girl, aged 11, entered the Peter Bent Brigham Hospital with a history of good health until three months before admission, when there developed a marked nervousness and loss of appetite, followed rapidly by double vision, headache and vomiting, suboccipital pain and stiffness, convulsions, delirium and loss of vision.

Examination revealed marked suboccipital tenderness, stiffness of neck, a high choked disk with secondary atrophy, dilated pupils, bilateral sixth nerve paresis and marked hypotonia. There was no incoordination nor nystagmus. The reflexes were absent. There was marked convolutional atrophy. Following a negative suboccipital exploration, the child was discharged considerably improved by the decompression. This improvement did not continue and two months later she became very much worse. She then developed complete inability to void, necessitating catheterization three times a day for a week. Frequency and incontinence then developed and continued until her death three months after the operation.

Necropsy revealed a circumscribed tumor mass 2 cm. in diameter, occupying almost the exact center of the cerebellum, projecting into the fourth ventricle, and producing a marked internal hydrocephalus. Microscopic examination showed it to be an extremely cellular glioma.

CASE 7.—W. M., a boy, aged 11, seven months before admission to Lakeside Hospital began to complain of intense frontal headaches, suboccipital pain and frequent vomiting, occurring at intervals of a week. These difficulties were supplemented several months later by dizziness, staggering gait, occasional periods of unconsciousness and failing vision. In the two months preceding his admission the patient had marked difficulty in starting urination. His mother noted that he would not void for periods of from twelve to eighteen hours. When the attempt was then made, minutes would elapse before the stream came. Occasionally the first attempt would be given up entirely, and after from five to ten minutes another effort would be made, usually attended by completion of the act. Catheterization was never necessary.

Examination showed a greatly emaciated child, marked hypotonicity of all muscles, absent reflexes, dilated pupils, lateral nystagmus, a high-grade choked disk with secondary atrophy, slight ataxia of the right lower extremity, marked convolutional atrophy and suboccipital tenderness and rigidity.

At operation a cellular glioma was found situated in the midline, displacing the vermis and projecting into the fourth ventricle.

CASE 8.—M. L., aged 27, entered Lakeside Hospital with a complaint of double vision and inability to walk. Three months prior to her admission the patient had noticed a dizziness and staggering in walking. This became progressively worse so that she was unable to walk or stand. Accompanying the staggering, there developed a diplopia on looking at distant objects. Subsequent to the onset of these troubles there occurred two very severe attacks of headache with nausea but no vomiting. She noted also an increasing difficulty in picking up objects with her right hand, without any decided weakness. There occurred occasional attacks of tinnitus in the left ear, with a diminution, but not loss of hearing in that ear. There developed also some thickness of speech, and a slight difficulty in swallowing. Simultaneous with the onset of staggering gait, she noticed a great difficulty with urination. She felt a desire to void but could not start the stream. By drinking a large amount of water to the point of actual suprapubic and pelvic discomfort, she was able to void. During the previous year she had been troubled with obstinate constipation which had become progressively worse.

Examination revealed a positive Romberg sign, an inability to walk alone, with an evident weakness of the right leg, a well sustained lateral and vertical nystagmus, a complete loss of vestibular sense on the left side, as shown by the Bárány tests, a left corneal areflexia, a diminished gag reflex and a marked suboccipital tenderness on the left. There was no papilledema.

At operation a large cholesteatoma of the left cerebellopontile angle was disclosed, which was partially removed.

SUMMARY

Experimental evidence is available indicating the localization in the corpus subthalamicum of a center for the control of contraction of the bladder.

Eight cases of cerebellar tumors occupying the midline, or distorting the midline structures by their size, are presented in which voluntary micturition was either delayed or temporarily abolished. It is suggested that this difficulty of micturition may be explained on the basis of an interruption of the nerve fiber bundles passing from a micturition center to the lower spinal cord segment in the sacral region, whence impulses reach the bladder through the nervi erigentes. These cases may be considered as furnishing evidence that the voluntary act of urination is initiated by impulses which originate in the brain, possibly in the subthalamus, and reach the bladder through the nervi erigentes, and that the first event in the process of micturition is an activation of the detrusor urinae with relaxation of the sphincter.

News and Comment

FIFTY-SECOND ANNUAL MEETING OF THE AMERICAN NEUROLOGICAL ASSOCIATION

The next meeting of the American Neurological Association will be held in Atlantic City, June 1, 2 and 3, 1926, in the Hotel Ambassador.

THE NATIONAL ASSOCIATION FOR THE STUDY OF EPILEPSY

The next meeting of the National Association for the Study of Epilepsy will be held in New York in the Hotel Waldorf Astoria, June 7, 1926.

THE AMERICAN PSYCHIATRIC ASSOCIATION

The American Psychiatric Association will hold its next annual meeting in New York in the Hotel Waldorf Astoria, June 8 to 11, 1926, inclusive.

Abstracts from Current Literature

Ueber den Heutigen Stand der Aphasielehre. G. Mingazzini, Klin. Wchnschr. **4**:1289 (July) 1925.

Mingazzini in this article reviews some of the more recent advances which have been made in the field of aphasia. In 1906, Marie stated that Broca's area had nothing to do with the function of speech. He based this conclusion on two facts: one, the occurrence of motor aphasia without demonstrable lesion in Broca's area; two, the occurrence of lesions in this area without evidence of aphasia. Mingazzini takes opposition to Marie's statements. Regarding the first point, he feels that in diaschisis, in infectious diseases, in senile brain atrophies, etc., functional disturbances may occur in Broca's area even though no macroscopic lesion exists; also at times the pars operculum is poorly developed or may be deep seated so that no superficial lesion is noted. In reply to the second statement he argues that lesions of the anterior end of the lenticular nucleus may give aphasic symptoms, but this does not mean that Broca's area is not involved. Both Mingazzini and Henschen have shown by macroscopic and microscopic findings that lesions of the anterior portion of the lenticular nucleus may produce a similar syndrome to that of lesions of Broca's area. The author has shown by serial sections that lesions of the anterior third of the putamen produce aphasia, while lesions of the posterior two-thirds produce dysarthria or anarthria.

Mingazzini and Henschen believe that in childhood both the left and right Broca's areas are potentially for motor speech and that this fact accounts for the rapid recovery of motor aphasia during the developmental years. As time goes on, the left third frontal convolution takes over the function of the right side so that repair in advanced years is much more difficult. It is on the basis of this bilateral representation that the author believes that tracts lead from the frontal convolution to the tip of the lenticular nucleus, which represents the neophylectic zone, and that these zones are connected by fibers passing through the corpus callosum. The major portion of the articular fibers from the putamen join the corticobulbar fibers, then ascend to the knee of the internal capsule and to the median fifth of the pes pedunculi. They then ascend in the median lemniscus where they enter the motor nuclei of the facial, of the hypoglossal and probably also of the vagus nerves. It is fairly well established that not only has Broca's area to do with motor aphasia but that interruption in the fiber tracts to the lenticular nucleus will also produce the same clinical picture. Cases to demonstrate this point have been examined anatomically by the author. Henschen's numerous cases corroborate the findings of Mingazzini.

For some years it has been believed by various observers that Broca's area has some association with Wernicke's zone and that by this means memory pictures are translated by association fibers into auditory word pictures. A disturbance of this association produces an auditory word aphasia in which words are missed, but some stimuli come from the right side and the lesion is not total. If the lesion is on the right side very little disturbance is noted.

In the author's opinion, Broca's area has to do especially with motor word engrams of syllables rather than words of more than one syllable. For this reason, in ordered speech there must be an association of acoustic impressions to coordinate proper speech. Even in a child this failure of correct coordina-

tion produces incoherent words, as ting for ring, aet for paket and hinschen for kaninchen.

In deaf mutes in whom the acoustic area or association fibers are impaired, by painstaking practice motor images of syllables are learned by the direct use of the facial and lingual muscles, and for this reason speech is confined to words of one syllable for a long time; the association of several syllables is extremely difficult. This fact helps to demonstrate the need of acoustic pictures for the production of fluent speech. This relationship between Broca's area and Wernicke's zone is most important, but does not detract from the definite function of Broca's area as a motor speech zone.

Turning to the graphic center, it appears that Mingazzini, Marie and also Henschen locate this area in the foot of the second frontal convolution on the left side. They ascribe to it the dignity of a true center, while Dejerine considers writing only a higher motor act of the hand, and points out that a person can write with the elbow or foot. Henschen maintains, as a result of his pathologic-anatomic studies, that a graphic center exists. To this center he ascribes a higher exactness in graphic movements than exists in the motor area. To Broca's area he ascribes also a higher psychic dignity as director of a motor zone having to do with the movements of the mouth and tongue apparatus, and where impulses for the execution of words arise. From the graphic area fibers extend to the putamen as in the case of Broca's area. There is also a close connection between the auditory word and optic word components, as they all have a close association in writing. Because of the necessary kinesthetic sense involved in writing, apractic disturbances may readily occur.

Henschen recognizes the following forms of agraphia: (1) due to lesions of the reading center (angular gyrus); (2) due to lesions of the auditory word center (temporal lobe); (3) due to lesions of stereognostic centers (parietal lobe). In addition to these, Henschen recognizes two other forms: One a result of lesions of the dorsal portion of the occipital lobe in the region connecting the interparietal fissure and the imaginary extension of the parietal occipital fissure; to this region he ascribes the function of visual word pictures which when injured produces an agraphia; because of its close proximity to the reading center and the visual center there is a close relationship between agnosia, alexia and occipital agraphia. The other form, evolved as a result of Henschen's work, is that resulting from lesions of the island of Reil and basal ganglia; Henschen has designated this as conduction agraphia; he believes that the external capsule contains fibers which connect the various centers by association tracts.

Henschen has also noted that in lesions of Broca's area when aphemia and agraphia coexist, the agraphia gradually disappears if the lesion is confined definitely to this area. This is contrary to the Wernicke-Lichtheim theory in which it is maintained that the aphemia and agraphia both result from the same lesion. Henschen is of the opinion that when agraphia and aphemia coexist the lesion has extended into the subcortical substances and has interrupted fibers from Broca's area to the second frontal convolution; in other words, the agraphia is a conduction agraphia.

As a result of Wernicke and Dejerine's work the presence of a reading center is disproved. The work of Henschen, however, indicates that in lesions of the left angular gyrus word blindness appears. His work also shows that arithmetical functions are more or less independent of speech though anatomically closely allied. He states that the inability to write figures is not the result

of lesions in Wernicke's zone but the result of diffuse disturbances of the left frontal area. The use of words or figures represents two different psychic processes which utilize different anatomic mechanisms. The visual sense naturally is a big factor in arithmatical problems as noted in figure blindness. The auditory factor also enters into play in any such operation. In arithmetical problems motor speech components are important, as it is necessary to follow the problem with the motor images of the figures. Therefore, in motor aphasia arithmetical problems are good tests to be employed.

Musical speech undoubtedly utilizes different association centers and tracts from those of normal speech. It would seem that a center for vocalization exists in the inner border of the pars triangularis of the left third frontal convolution and the music sense in the temporal lobe.

After one has considered all that has been said regarding the various anatomic centers of the components of speech, one cannot fail to come to the conclusion that much remains a mystery. It remains for the clinician and anatomist to unravel more of this problem, as was so well done by the masters Broca and Wernicke.

MOERSCH, Rochester, Minn.

SELF-MUTILATION. HEINZ HARTMANN, Jahrb. f. Psychiat. u. Neurol. **44**:31, 1925.

A woman, aged 56, married, was admitted to the Wagner-Jauregg Clinic on May 6, 1923, with the history that for the last three months she had been depressed, anxious and unusually lachrymose: She also complained of weakness and pains in the head and abdomen, and refused nourishment. She was married at the age of 31, but never loved her husband. Although she was extremely passionate, she had had no coitus for the last six years, and for seven years prior to this she practiced coitus interruptus.

In 1900, she had been a patient in the same clinic. At that time her husband stated that she had always been extremely nervous, irritable and stubborn, and that she had insomnia and complained of pains in the precordial region. Some days before admission she was discovered to have a tapeworm, and she became unusually worried lest her "abdomen should have to be opened" to remove the parasite. After this she developed a manic episode during which she first pulled down from the wall a picture which she tore, and then she gouged out her left eye with her fingers. When brought to the clinic she was at first quiet, but very soon became restless, and began to cry and to beat herself. She then began to speak to imaginary persons. She apparently had hallucinations and she responded to questions only at times. She insisted that she must "take out" her remaining eye. When asked why she gouged out her left eye, she said that she "had to do it." She insisted that she was in a convent and not in a hospital. Two days later she asked for a scissor in order to "bore out her eye." At the end of a week she became quiet and tractable, but began to reproach herself for her previous bad conduct. She said that she had always been bad, and especially so to her parents; she could not get herself to pray because she ceased to believe in God; she felt, therefore, that she had to make some sort of sacrifice, especially when she reminded herself of the biblical passage "and if thy right eye offend thee, pluck it out from thee and cast it from thee"; it was then that she decided to "blind herself." She sought approval for her act in the fact that while looking at a picture of Christ that was hanging directly over her bed she saw "Christ winking at her." During the next six weeks she was continuously praying, and begged that a priest be sent to her; she wanted to "offer further sacrifices

to the Almighty." She remained in the asylum for four months. After her discharge she remained well until 1902, when, after a severe illness of one of her children, she became excited, and was brought back to the clinic in a manic state, but not until she had again made several attempts to enucleate her right eye. Immediately after her admission she lapsed into a depression for which she was transferred to the asylum, where she stayed for a few weeks. She remembered every detail of her first sojourn in the institution. Her somatic examination was entirely negative, and as her depression cleared up, she was discharged as cured.

On her last admission (1923) she volunteered a description of her first attack, with a correct reproduction of every detail. She remembered that she was in such a state of anxiety that she felt that something unusual must happen; she reproached herself for her frequent masturbation, which she began at the age of 4 years, or perhaps earlier, and which she continued up to her marriage. While at school she considered herself very unfortunate because she could not control her desire to masturbate. She felt especially bad about this when she began to receive religious instruction. She also reproached herself for being disobedient to her parents and for giving them much trouble. The enucleation of her left eye she explained as follows: She tore down a picture of Christ which hung over her bed; she pressed the picture against her bosom and began to kiss it incessantly, during which she became very excited and while her mother had left the room to obtain assistance she "pushed" the left eyeball out of its socket with her fingers. The act was not painful. To the left of her she saw a golden figure 20 cm. in height, and as she put her hands up to her eyes she saw the figure "nodding" to her; she then felt that she had "to sacrifice her eye to Christ"; she always experienced a "great sensation of love for that Saint"; "he was the protector of her family." Her grandfather's name was Joseph. On her wedding day, "instead of dedicating candles to Mary she dedicated them to Joseph." She continually addressed an old gentleman whom she saw in the asylum as Joseph. When asked why she had enucleated her eye, she said: "One sins mostly with one's eyes during such phantasies." When asked about her sex life, she volunteered that "looking" always excited her, it stimulated her "sensual love"; she had to "look away" quickly when she saw a man, otherwise she would become very passionate. As a child she slept in the same bedroom with her parents; her father was never ashamed to be exposed in front of her, for which he was always upbraided by her mother; on numerous occasions she saw her father's genitals; when her parents were in bed she heard the bed creak; at first she did not realize the significance of this, until her father scolded her for "always watching"; it was then that she began to realize what was going on. After her marriage her sexual desire was always greater than that of her husband, and lately she had been unusually passionate.

Hartmann assumes that the psychosis from which the patient was suffering was the basis for her tendency to inflict punishment on herself, which she actually accomplished during her first episode by gouging out her left eye. The analysis established the fact that the idea to blind herself was also the psychologic motive for her imperative impulse to repeat the act during her second episode. As happens in all cases of self-mutilation, the psychologic determinants in this case may be said to be, first, the premature hypersexuality and second, the tendency to "look." The latter was greatly aroused by the patient's "seeing" her father's genitals and by her witnessing the sexual act consummated by her parents in her presence. There can be little doubt

but that her father played a great dominating rôle in her childhood, and in her delusions she substituted for her father Joseph, whom she regarded as the protecting patron of the family. She felt herself greatly attached to this saint, and it was the sight of his image that dominated the clinical picture of the first episode of her psychosis, particularly in relation to self-mutilation; she was experiencing the same affective states which she had originally associated with her father. Finally, this tendency to self-mutilation was a projection mechanism perceived as a command from an image which she saw during her hallucinations.

KESCHNER, New York.

CHRONIC SUBDURAL HEMATOMA. ITS PATHOLOGY, ITS RELATION TO PACHYMENINGITIS HEMORRHAGICA AND ITS SURGICAL TREATMENT. TRACY JACKSON PUTNAM and HARVEY CUSHING, Arch. Surg. **11**: (Sept.) 1925.

This article deals in detail with the clinical course and pathologic results of ingravescent hemorrhage, chronic subdural hematoma. It has long been known that an apparently insignificant trauma to the head may in certain individuals be followed, after a latent interval which varies from a few hours to months or even years, by symptoms of cortical irritation and of intracranial pressure due to a subdural hematoma. The clinical history of eleven cases is outlined from the experience of the authors and other members of the Society of Neurological Surgeons. Clinically, after a period of headache, these patients show an extraordinary variability of symptoms, particularly in the intellectual sphere. They are prone to psychoses and often become irritable, indecent and unmanageable. Choked disk is apt to be present and a frontal lobe tumor suspected.

At operation or necropsy, a subdural hematoma will be found on one or both sides enclosed in a continuous membrane slightly adhering to the dura but not adherent to the arachnoid. The enveloping membrane on the side toward the arachnoid is thin and covered with mesothelium. On the dural side, it is more dense and composed of organizing granulation tissue in which are large mesothelium lined spaces containing blood and fibrin which appear to anastomose with each other and with the capillaries.

In this respect, the membrane of the traumatic hematoma seemingly differs from that of the commonly described pachymeningitis hemorrhagica interna ,in which the thin-walled vessels are enormous, and no mesothelium lined spaces are seen. Such a pachymeningitic membrane may possibly give rise to hematomas, which symptomatically and in the gross resemble the post-traumatic variety.

In certain cases in which the onset of symptoms is delayed for only a few days after trauma, it is possible that they may be due to a hematoma formed immediately but which only announces its presence when the brain becomes edematous or congested. In other cases, the occurrence of late hemorrhages seems probable and may be due to the formation of communication between the mesothelium lined spaces and blood vessels, with rupture of one or the other.

The spontaneous pachymeningitis vasculosa may represent a chronic form of the same process. There is no satisfactory evidence that either form is inflammatory or neoplastic. The term reactive pachymeningitis might be used to designate the peculiar process of organization that is evoked by the presence of blood clot or other collection of fibrin on the inner surface of the dura, and which may possibly give rise to secondary hemorrhages.

When the presence of a subdural hematoma is suspected, an exploratory craniodural puncture over the hemisphere will give the most reliable evidence of the presence or absence of the clot. The puncture should be made on both sides, as the lesion is not infrequently bilateral. Lumbar puncture may show a faintly xanthochromic fluid, but often the cerebrospinal fluid is negative. If the diagnosis is verified, an osteoplastic resection with reflection of the dura and removal of the more or less organized clot as intact as possible is the procedure of choice, with subsequent painstaking hemostasis. The removal of the dura on the basis that it is a possible source of further hemorrhage is unnecessary. Experience tends to show that there need be no fear of reformation of the clot, but that cerebral edema is apt to occur in the brain released from its long pressure. It consequently may be advisable to combine the osteoplastic exploration with a subtemporal decompression. Should edema occur, the use of hypertonic saline solution or the performance of lumbar puncture should perhaps be resorted to before reinvestigation of the wound, for in no case in the present series at least has the procedure been of use.

GRANT, Philadelphia.

REPORT ON THE PATHOGENESIS OF THE HEMICRANIA. PASTEUR VALLERY-RADOT, Rev. neurol. **1**:881 (May) 1925.

In a clear and complete exposition of our knowledge of the hemicranic syndrome to which he contributes many personal views, the author establishes the limits of the hemicranic syndrome: headache, generally of the hemicranic type, arising as a crisis and accompanied by photophobia, vertigo, nausea, vomiting and vasomotor manifestations. Hemicrania is then a series of crises intercalated by periods of welfare. The author recalls the old and new theories invoked to explain the syndrome: cerebral neuralgia (Romberg), lesions of the cortical cells (Moebius), exaggerated sensibility of the sensorial centers (Schottin), temporary increase of the hypophysis volume (Fisher and Hodges), temporary increase of the cerebrospinal fluid pressure (Lowenthal), neuralgia of the intracranial branches of the trigeminus (Eulenburg), myositis of the neck muscles (Hartenberg-Muller) and, finally, the vasomotor theory (du Bois-Raymond, Claude, Sicard, Laignel-Lavastine).

The author favors the vasomotor theory, to sustain which he recalls some of the symptoms accompanying the crisis, as pallor of the face; contraction of the temporal artery; sensation of constriction at the temples; transitory hemiparesis, paraphasia and visual disturbances and simultaneous onset of hemicrania and vascular spasms of other regions (retinal artery). On the other hand, from the experimental point of view he points out how the inhalation of vasodilator substances, as well as periarterial sympathectomy, may have a favorable influence on the course of the crisis. The vascular angiospasm of the ophthalmic and dural branches of the trigeminus explains the simple hemicrania; the angiospasm of the calcarine region, the ophthalmic hemicrania and the angiospasm of the rolandic regions, the so-called associated hemicrania.

The causes acting on the sympathetic nervous system, responsible for the vascular changes may arise from: (*a*) Anaphylaxis. Pagniez, Nast and Vallery-Radot have already shown the coexistence and alternation of hemicranic crises with anaphylactic syndromes (asthma, edema, paroxystic tachycardia). On the other hand, ingestion of special foods may start a crisis, which is wanting after anti-anaphylactic treatment. The similarity of anaphylactic crisis with the hemicrania attack (Pagniez and Nast, Van Leuven and Zeydner) and the positivity of skin reaction to some proteins (Harkavy-Vallery-Radot) are also

instanced. (*b*) Endocrine disturbances, which can be divided into ovarian, thyroideal and hypophysial. (*c*) Gastro-intestinal disturbances: after ingestion of special proteins, fat or food. (*d*) Reflex irritations. (*e*) Thermic disturbances. (*f*) Emotional upsets. Contributing causes such as insufficient sleep, alimentary disorders and atmospheric variations may be operative.

The mechanism of the hemicranic crisis may be set in action by: excitation of the sympathetic nervous system through the intermediation of a colloidoclastic shock; direct excitation of internal or external origin. The sympathetic nervous system in hemicranic subjects may be found in a condition of congenital lessened resistance, but at times it is an organic disease, such as dysfunction of an endocrine gland, which is responsible for the disequilibrium of the vegetative nervous system. The abdominal sympathetic system may also be involved during a crisis.

That hemicrania appears in the form of a crisis is explained by the fact that during the intervals the organism, by means of an unknown mechanism, gradually enters the condition in which the exciting cause will bring about an outburst. From the biologic point of view, two chemical findings which almost constantly accompany the crisis are: hypercholesterinemia, and alkalinity of the blood. In conclusion, the author contests the identity, suggested by some authors, between the epileptic and the hemicranic crisis; he considers that only analogy and not identity may be established between the two syndromes.

FERRARO, Washington, D. C.

THE DISCOVERY OF HISTOLYSIS IN THE NERVE CENTERS OF INSECTS. D. SANCHEZ, Arch. de Neurobiol. **4**:289, 1924.

Sanchez reviews the literature on the subject and points out that histolysis had not been described in the nerve centers of insects during metamorphosis, the accepted idea being that the nervous system of the imago is the continuation of that present in the larva. His own investigations on the nerve centers during metamorphosis of several butterflies and moths show the presence of histolysis and he reviews and discusses at length the facts which led to its discovery.

The slides were stained with Golgi and Cajal's methods and with hematoxylin. The process of histolysis begins during the transformation of the caterpillar into pupa and is manifested in the formation of irregular lacunae within the ganglia. These lacunae first appear in the frontal portion of the cerebral ganglia advancing from this area toward the ventral and posterior surfaces of the brain. They are occupied by a clear fluid containing leukocytes, a few large granular corpuscles and abundant minute granules; in some cases there are also tracts of connective nature which may assume the form of a network the meshes of which were apparently occupied by cells. These structures are not found in the caterpillar before pupation. The size and extent of the lacunae varies according to the stage of pupation.

As the transformation of the caterpillar into a pupa advances there appear one or two empty spaces around the superior portion of the esophagus, between the neurilemma and the inner ganglionic mass, which appears corroded as if many of its cells had disappeared. Along with these changes there is degeneration of the nerve cells. Degenerative changes are manifested in the paleness of the whole cell, the scarcity of the cytoplasm, which appears shrunken, and the small size of the nucleus which often shows an irregular shape. In a more advanced stage of pupation there are rather extensive zones — especially

in the central portion of the cerebral ganglion — which are deprived of nerve cells; these wide lacunae are also filled with clear fluid rich in eosinophilic granulations. The latter seem to be due to protein coagulation and vary somewhat in shape and size, being derived, it is believed, from destroyed ganglionic portions. Around these zones there are still some nerve cells, isolated or forming small groups. Most of these elements are undergoing degeneration; their outlines appear irregular, somewhat diffuse, and they possess pale cytoplasm of fibrillar aspect and a shrunken nucleus which is sometimes fragmented.

After discussing in detail the origin and significance of the lacunae within the ganglia, the author considers the mechanism of histolysis without expressing an opinion as to the way it is accomplished. He suggests that phagocytosis may play an important rôle but, at the same time, he expresses the opinion that phagocytes may not be able to destroy the nerve cells until the latter have undergone degenerative changes. The article ends with a description of the diverse cell types present in the slides. Some of these cells are derived from nerve cells and they represent either active elements originated through division, or cells in different phases of degeneration. Other cells seem to represent phagocytic elements producing disintegration of the nerve tissues. Among the latter there are large granular cells, termed neurophages or macroneurophages if of large size, other elements with clear cytoplasm, true leukocytes and polynucleated cells which seem to represent elements in active phagocytosis.

NONIDEZ, New York.

SOFTENING OF THE SPINAL CORD DUE TO LYMPHOGRANULOMA IN THE EXTRADURAL SPACE, WITH LYMPHOGRANULOMA OF THE UTERUS AS AN ACCESSORY FINDING. K. M. WALTHARD, Ztschr. f. d. ges. Neur. u. Psychiat. **97**:1 (June) 1925.

Neither Lewandowsky nor Oppenheim in his textbook mentions lymphogranulomas as causes of cord lesions. Kaufmann gives them as a cause of cord pathologic change by compression of the vertebrae, as in a tuberculous spondylitis. Ziegler, in his monograph on Hodgkin's disease, says that spastic paraplegia may result from cord compression and the production of a transverse lesion. Recently, Luce has reported two cases of lymphogranuloma of the spinal cord and quotes two cases of Nonne and Simmonds. Düring, Askanazy and Weber also have each reported a case.

The case detailed in this paper is from Spielmeyer's clinic. The patient, a woman, aged 53, previously in good health, was suddenly taken ill with severe pain in her back radiating to the left shoulder blade. She had no fever and roentgenograms were negative. During the next thirty-six hours she developed a complete paraplegia of the lower extremities with incontinence of feces and urine, and complete anesthesia up to the third thoracic level. Decubitus and pyelonephritis followed and she died at the end of three weeks.

Necropsy showed no spinal caries. In the lower cervical segments was an area of softening in the central parts of the cord, measuring 4 cm. in diameter. From the third thoracic segment to the lumbar cord no vestige of spinal cord was present — the entire organ was made up of brown, chocolate-colored, pulpy masses. Microscopically, the upper parts of the cord were normal. The softening began at the sixth or seventh cervical segment; it involved the dorsal columns, was sharply demarcated, and did not involve the commissure. The central canal was obliterated; the anterior horns were intact. At the second dorsal level, the destruction was almost complete with thrombosis of

the vessels. Lower down was a picture of a complete transverse lesion with almost complete loss of the topography; the dorsal columns were entirely destroyed; parts of the lateral columns were intact, and the gray substance was left only in parts. This extent of lesion involved almost the entire thoracic cord. Down to the sixth dorsal segment blood was found only in the vessels; at the ninth dorsal it was present in the zone of softening. In the intradural space was found a granulation network consisting of lymphocytes, epithelioid cells, fibroblasts and giant cells. The sharply limited necrotic areas were filled with fat and blood, and the vessel thrombi were made up of the granulation substance alone. No eosinophil cells were found. The lymphogranuloma enveloped in fat, began at the third thoracic segment; it was outside of an not connected with the dura. It was sharply demarcated. It was divided into two parts longitudinally, and between these was a small hemorrhage.

The cell picture found in the tumor corresponds to that of the lymphogranuloma of Hodgkins disease, except for the absence of eosinophil cells. Lymphogranuloma does not always begin in the lymphatic system; Teeplan described a case in which it was primary in the thyroid. Isolated involvement of the nervous system is not common; here the uterus was similarly involved. The case of Nonne is similar to that of Walthard in that the disease involved only the nervous system.

ALPERS, Philadelphia.

HEPATO-LENTICULAR DEGENERATION. STANLEY BARNES and E. WESTON HURST, Brain **48**:279 (Sept.) 1925.

Four children of the same family were studied clinically, and in two a complete histologic study was made. All four patients suffered from symptoms of cirrhosis of the liver or, as the authors prefer to describe it, repeated attacks of acute hepatitis, for a considerable period before the appearance of symptoms of lenticular disease, which were severe in two and mild in a third. The symptoms of progressive lenticular degeneration consisted of gradual loss of power, athetosis, muscular rigidity, hypertonus, dysarthria, dysphagia and slight emotional changes. In one of the children, who had marked cirrhosis of the liver, there were no symptoms of involvement of the nervous system.

In the case of the patient with marked lenticular disease, pathologic examination revealed pronounced shrinkage of the putamen with the microscopic findings of neuronal degeneration, neuroglial overgrowth and new formation of capillaries. Considerable nerve cell degeneration had likewise taken place in the cortex and in the caudate nucleus, but with only slight neuroglial proliferation in the latter areas; the globus pallidus, the cerebellum and, to a less extent, the optic thalamus showed alterations from the normal. Examination of the liver showed a condition of multilobular cirrhosis. In the case of subacute hepatitis without nervous symptoms, pathologic examination of the nervous system revealed no gross changes in the lenticular nucleus, but microscopically there was a definite outfall of the large nerve cells of the putamen and degeneration of all remaining elements both large and small. While the changes were considerably more advanced here than in other regions, the cortical neurons and those of the caudate nucleus, as in the preceding case, were also affected. There was nowhere any gross increase in the number of neuroglial cells, but those present were hypertrophied. The authors emphasize that in both cases signs of inflammation were completely lacking in the nerve tissue; in other words, the process appeared to be a toxic degeneration with disappearance of nerve cells accompanied by neuroglia reaction. The liver

presented an unusual and suggestive picture, that of healing, subacute yellow atrophy. Plasma cells were present in the fibrous tissue strands, suggesting an inflammatory basis for the condition. The existence of liver disease in all four members of this family, of whom two subsequently developed well marked nervous symptoms and a third had definite pathologic change in the nervous system without nervous symptoms at the time of death, leads the authors to conclude that in hepatolenticular degeneration the liver disease is antecedent to the nervous damage and consists of a series of attacks of acute inflammation (hepatitis) at irregular intervals. They state that the toxin enters the circulation and causes fresh nervous destruction only during the acute attacks and not during the remissions, despite the fact that the cirrhosis of the liver may have become permanent. The toxin causing the heptatitis is thought to be of bacterial origin and to arise in the alimentary canal. Logical reasons are advanced to suggest that Wilson's "progressive lenticular degeneration," Gowers' "tetanoid chorea," certain cases of "pseudosclerosis" and Thomolla's "torsion spasm" should be grouped together as forms of hepatolenticular degeneration.

STACK, Milwaukee.

LESIONS OF THE SCIATIC NERVE FOLLOWING INTRAGLUTEAL INJECTIONS OF QUININ. JOSEF WILDER, Jahrb. f. Psychiat. u. Neurol. **43**:215, 1924.

This paper is based on four cases with atrophy, paralysis, sensory disturbances, reflex changes and electrical changes in the region supplied by the sciatic nerve. All four patients had lived in Palestine, where malaria seems to be endemic and where the usual treatment consists of intragluteal injections of quinin. One of the patients stated that he knew of twenty similar cases in the immediate vicinity where he had been living. Wilder also points out that in Italy, where malaria is also treated by intragluteal injections of quinin, sciatic lesions following these injections are not rare. Nerve complications are also reported following intragluteal injections of soluble and insoluble salts of mercury, ether, alcohol, arsphenamin, superosmic acid and antipyrin; they follow intramuscular as well as perineural injections. The author is convinced that these complications are not due to trauma to the nerve nor to the effect of pressure by the injected fluid on the nerve; he is inclined to attribute them to one of two causes: (1) (rare) an injury to the nerve from the hemorrhagic effusion in its vicinity, and (2) the more frequent toxic and inflammatory effect of the injected substance. As innumerable injections of mercury, quinin and even 50 per cent. antipyrin solutions are given daily throughout the world without causing such untoward effects, the question is raised, as to what factors produce these complications in one patient and not in another. It cannot be that some patients are more susceptible to the drug than others, because experience has shown that in some cases no such complications have occurred in the same patient until the twentieth injection of a series has been given, and there was no recurrence of the nerve lesions following a resumption of the injections after the disappearance of the evidences of the sciatic lesions. In his efforts to solve this problem, Wilder investigated, in addition to his four cases, a case by Janusch (quinin), one by Rindfleisch (intragluteal arsphenamin), one by Kühn (antipyrin), one by Böttiger (mercury) and one by Dopter and Tanton (mercury). In all of these cases the injection was given in the immediate vicinity of the nerve; the patients began to complain of pains or paresthesias directly while the injection was being given, and five of the cases showed evidences of an inflammatory

process (swelling and abscess formation); the latter were in the region of the sciatic or of its adjacent nerves (inferior gluteal, pudendal, posterior femoral cutaneous). Most of the patients also showed various sized infiltrates and swellings in the skin and muscles. Owing to the fact that all of the substances mentioned give rise to slighter inflammatory phenomena when injected intramuscularly than when injected subcutaneously, Wilder believes that the crux of the problem is the selection of a proper site for the injection. He, therefore, suggests that the injection be given above a line drawn between the upper margin of the great trochanter and the rima ani; he also prefers the neutral salts of quinin, although he states that it remains to be seen whether the parasiticidal effect of these salts is the same as of the other preparations.

KESCHNER, New York.

MORPHOGENESIS OF THE CEREBRAL AQUEDUCT. LUIGI CASTALDI, Arch. gen. di neurol., psichiat. e psicoanal. **6**:157 (Oct.) 1925.

No author has so far reported a systematic study of the transformations which the Sylvian aqueduct in mammals undergoes during the period of development. This research fills an obvious gap. Castaldi chose *Cavia cobaya* as material for his investigation. In order to follow the transformation of the mesencephalic cavity he studied sections at different stages of prenatal life, and also made four complete wax reconstructions of embryos 8, 11 and 22 mm. in length, respectively, and of an adult animal; in addition, he made a partial reconstruction in a fetus 88 mm. long. A review of previous work and a comparative study of the cerebral aqueduct precedes the report of the original work.

The measurements of the aqueduct at the different embryonic stages and in the adult are given in the accompanying table.

Measurements of the Cerebral Aqueduct at the Different Embryonic Stages in the Adult Cavia Cobaya

	8 Mm.	11 Mm.	22 Mm.	88 Mm.	Adult
Length	2.35	2.4 (2)	4.7 (2.5)	....	3.7 (3.1)
Width	1.45	1.70	1.20	1.25	from 0.40 to 1.05
Height	0.70–1.20	0.90	0.40	0.68	from 0.45 to 0.75

The author confirms the findings of Ziehen in *Erinaceus* as given by Gronberg, although this author does not state the epochs in development at which the specimens were taken. There is first an increase in size of the mesencephalic ventricle together with the increase of the mesencephalon, and then a diminution. In other words, at a certain period of development the cavity no longer increases, even in absolute size, although some dimensions (height) seems to gain between the stage of 22 mm. and that of 88 mm. In the adult the total capacity is smaller than in embryos of 22 mm., in spite of the great increase in the size of the mesencephalon. The cavity of the mesencephalic ventricle is reduced by the growth of adjacent structures, especially by the growth of the roof, which causes an increase in thickness of the alar plates which grow at the same time toward the external surface and toward the mesencephalic cavity. The mesencephalic ventricle constitutes at first a great part of the encephalic cavities; then the aqueduct becomes relatively smaller than the four encephalic ventricles, not only on account of its absolute diminu-

tion in size, but also because the mesencephalon in toto grows much less than the other encephalic segments.

The conformation of the cerebral aqueduct in the adult *Cavia cobaya* shows characteristics which are dependent on prenatal dispositions; the intermediate ventricle (dilatation of the dorsal portion alone) forms the lateral recesses, the dorso-caudal culdesac for the funnel-shaped passage to the fourth ventricle forms the posterior recess and the carina and the other peculiarities of the ependyma of the vault form the caudal extension of the subcomissural organ.

NACCARATI, New York.

THE NERVE-ENDINGS IN THE PANNICULUS CARNOSUS OF THE HEDGEHOG, WITH SPECIAL REFERENCE TO THE SYMPATHETIC INNERVATION OF STRIATED MUSCLE. HUGH SHAW DUNN GARVEN, Brain **48**:380 (Sept.) 1925.

The author presents an extensive review of the literature, especially of the work of Boeke, Hunter, Sherrington and Kulchitsky, on the structure of muscle fiber and its innervation. He then reports the results of an investigation of this complex mechanism using the panniculus carnosus muscle of the hedgehog, studied by the gold chloride method. The following results were obtained: The muscle fibers show varying degrees of longitudinal striation and varying contents of sarcoplasm, but cannot be divided into two definite classes as others have contended. The motor end-plates in these fibers show great differences in size, form and shape, but cannot be classified into different types. The individual muscle fibers are plurisegmentally innervated; all fibers, whether rich or poor in sarcoplasm, appear to be innervated in exactly the same way, and it is certain that sarcoplasm-rich fibers are innervated by medullated nerves. The author states that in the panniculus carnosus he finds no muscle fibers which do not have a medullated nerve fiber ending on them. The nerves entering the muscle contain a large number of nonmyelinated fibers, called by the author accessory fibers, and they end in the muscle fibers; they were seen in several cases to end on a muscle fiber which was also supplied by a medullated nerve. The author, therefore, concludes that there is a double innervation, somatic and sympathetic, of individual muscle fibers. This is in accord with Boeke's findings, but contrary to those of Hunter who claims there are two types of muscle fibers, one having a somatic and the other a sympathetic supply. The accessory fibers are found to pass to the capillary wall, and two different routes of nerve supply to the capillaries are demonstrated, one by extension from the arteriole, and the other direct by way of the motor nerve fibers. The author is convinced that the nonmyelinated or accessory fibers that go to the capillary wall and to the muscle fiber are of the same, namely, sympathetic origin. In one instance, one branch of an accessory fiber was seen to go to the muscle fiber and another branch to the capillary wall. It is suggested that the function of these nonmyelinated nerves to the muscle fibers may be of a vasomotor nature. The author favors the theory put forward by Langelaan, that the plastic component of muscle tonus is a property of the sarcoplasm and is under control of the sympathetic system; and that the contractile component of muscle tonus is the property of the striped apparatus of the fiber and is under control of the cerebrospinal system. In the study of the spindle muscle fibers, it was found that their plate endings were formed from definitely medullated nerve fibers. A study of the muscle fibers in the frog, lizard and man, showed but little difference from those of the hedgehog; accessory fibers were seen in all.

STACK, Milwaukee.

THE INVESTIGATION OF SOME OF THE CAUSES OF INSANITY. SIR FREDERICK W. MOTT, J. Ment. Sc. **71**:631 (Oct.) 1925.

This presidential address before the Medico-Psychological Association of Great Britain and Ireland begins by calling attention to the comparatively great susceptibility of the highest levels of the brain to doses of narcotics which do not affect lower levels. It continues with a consideration of the influences of all the glands concerned in the function of reproduction. Especially is described the influence of the male hormone for the six months just before and after birth on all somatic cells, so powerful that after infancy in the male no such action is required. In the female, however, the corresponding hormone must continue to be formed in order to maintain female characters.

Changing his attack, the author states that his inquiries concerning relatives in the London County Asylums show the importance of heredity and the special liability to psychoses and neuroses at times when the sexual function waxes and wanes and during child-bearing and lactation. In these last cases the more extrinsic the cause, the better the outlook.

An explanation of manic-depressive psychoses follows in Hughlings Jackson's terms. We must look on the delusion and extravagant conduct as positive signs of activity in what remains intact of the highest levels; these imply negative states of defective perception and less adaptation to present surroundings. A similar set of positive and negative symptoms is brought about by alcohol. The highest inhibitory level may be useless because its synapses are dissociated, and the next perceptional and ideational level, if partly dissociated, may overact with that part of it which remains nearly intact. If all of this second level is damaged by a toxin, then we have a catatonic stupor.

An explanation of dementia praecox is found in a progressive suspension of function in certain neurons, due to germinal lack of durability in dementing cases, and to synaptic dissociation caused by temporary influences in recoverable cases. Hypofunction of the whole body is seen by the author in the greater susceptibility to infections and in atrophy of the reproductive organs and of the pituitary and suprarenal glands.

BOND, Philadelphia.

THE RELATIONS OF THE CORPUS STRIATUM AND THE PALLIUM IN VARANUS, AND A DISCUSSION OF THEIR BEARING ON BIRDS, MAMMALS AND MAN. WILLIAM HERMAN, Brain **48**:362 (Sept.) 1925.

This is an anatomic investigation of the three parts of the striatum and its pallial connections in varanus, carried out in the laboratory of Dr. Kapper, whose work along similar lines is frequently quoted. The author found that the neostriatum in varanus, the homologue of the putamen and caudate nucleus in mammals, arises partly from the pallium and partly from the base just anterior to the paleostriatum; by its union with the pallium and its identical structure, the anterior and dorsal portion of the neostriatum is clearly shown to be part of the pallium. The neostriatum is divided into a ventral and a dorsal portion by a fiber tract which passes from the pyriform cortex, hooks under the anterior and lateral aspect of the ventricle and sends its fibers into the dorsal portion; this tract is called the tractus corticoneostriaticus. According to the author, it reveals an unmistakable connection in varanus between the cortex and neostriatum; the ventral portion of the neostriatum receives the afferent thalamic fibers. The archistriatum, homologous to the amygdala in mammals, is entirely pallial in origin and is marked off from the neostriatum by

the fissura neo-archistriatica. It lies posterior and lateral to the neostriatum and receives the great mass of tertiary olfactory fibers forming the tractus cortico-archistriatica. Efferent fibers were also seen passing from the archistriatum in the forebrain peduncle to the thalamus. The paleostriatum is entirely basal in origin and lies directly ventral to the neostriatum and archistriatum. It receives fibers from the tractus thalamostriaticus, and its efferent fibers run in the basal forebrain bundle linking the paleostriatum, by way of the hypothalamus, with the midbrain.

In view of the definite anatomic connection between the pallium and the neostriatum in varanus, the author calls attention to the pathologic changes reported by others in the cortex and neostriatum in Huntington's chorea, athétose double and senile dementia, as well as Minkowski's findings of definite anatomic connections between these two areas in higher animals. He suggests that there may possibly be an anatomic connection between the cortex and neostriatum in mammals and man.

STACK, Milwaukee.

A CONTRIBUTION TO THE KNOWLEDGE OF THYROIDEAL ALTERATIONS IN HEREDITARY SYPHILIS. E. MORELLI, Boll. d. Ist. Sier. Milan. **4**:215 (Aug.-Sept.) 1925.

For this histopathologic study, the author has examined the thyroid gland in three groups of cases. In the first group are the thyroids of children dying soon after birth, who had shown evident clinical and anatomopathologic stigmas of precocious heredosyphilis. In these cases the spirochete was found in the liver. In the second group are the thyroids of children who grew normally for a certain period of time, but who at a later age showed signs suspicious of syphilis, the presence of which was confirmed afterward by necropsy. In the third group are the thyroids of children in whom the Wassermann test was positive, but who showed no clinical signs during life and no anatomopathologic evidences of syphilitic infection at necropsy. The importance of this research lies in the fact that the author found not only the usual connective tissue proliferations, but also other important histopathologic changes. In the thyroids from patients with early hereditary syphilis, hyperplasia and anomalies in connective tissue distribution, altered structure of the organ, extensive epithelial degeneration and formation of abnormal colloid were found. In late hereditary syphilis, the thyroid was found to be less involved, but it was in a state of unstable equilibrium, liable to respond in an exaggerated manner to hypersecretory stimuli. There were structural changes but no connective tissue hyperplasia, and there might be epithelial desquamation and transudation of plasma instead of colloid secretion under excessive stimuli. Associated with a structure that indicates degeneration there is always, at distant points, suggestive evidence of vicarious hyperplasia.

NACCARATI, New York.

STUDIES ON THE EXTRAPYRAMIDAL SYNDROMES. A. WIMMER, Rev. neurol. **2**:281 (Aug.) 1925.

Starting with the description of a case of infantile torsion spasm beginning with fits of tonic spasms which constituted for five years the sole symptoms of the disease, the writer develops the idea of the possible existence of a striatal epilepsy. He bases his affirmation first on the conception of the epileptic fit as conceived by Binswanger, Fisher, Monakow, Frank, et al., who believed that the convulsive attack was due to a mixed involvement of cortical

and subcortical centers; secondly, on the peculiar tonic fits described by Wilson of supposed extracortical origin, and on the work of Krisch who recently described the relationship between epilepsy and the extrapyramidal syndrome. On the other hand, the author recalls the tonic fits described by Forster in the extrapyramidal syndrome, and the case of Stertz in which epilepsy and tonic rigidity were combined in a case which at necropsy showed atrophy of the neostriatum with neuroglial hyperplasia. He believes that some of the clonic components of the fits manifested by his patient may have a striatal origin. The cause of the lesions in the striatum, which he believes underlie the essential torsion spasm, may be an auto-intoxication having a special affinity for the striatum or an abiotrophy, in the sense of Gowers, of these ontogenetically and phylogenetically older infracortical motor centers.

FERRARO, Washington, D. C.

THE TREATMENT OF CEREBRAL TUMORS BY RADIOTHERAPY. ROUSSY, LABORDE and LEVY, Rev. neurol. **2**:129, 1924.

The authors report five cases of brain tumor proved by operation or at necropsy. The condition in all was well advanced and most of the patients had undergone previous operative procedures. The details of the therapy were similar to those noted in the preceding abstract. The dosage was heavier, however, from 12,000 to 20,000 R being given. The first tumor, a meningeal growth the size of an orange, when removed at necropsy showed enormous nuclei, possibly the effect of the irradiation. In the second case there was a large cystic glioma of the cerebellum, symptoms of which had been present for four years. The third patient had a large glioma of the pontocerebellar region. His symptoms had begun some twelve years previously. The fourth tumor had given symptoms for seventeen years, and was found at operation to be a huge glioma of the right frontal lobe. The fifth patient, a woman, aged 29, had suffered from headaches since the age of 8, and from jacksonian seizures since the age of 12. Operation disclosed a slow-growing infiltrating growth that could not be removed. Roentgen-ray therapy in all these cases seemed to have no beneficial effect, but rather the reverse, the headache increasing, vomiting developing, vision failing and psychic symptoms undergoing intensification. The treatment was frequently interrupted and the dosage diminished in order to obviate these unfavorable effects. In no case was any permanent benefit observed.

FREEMAN, Washington, D. C.

ACTION OF OCCASIONAL CAUSES AND INCOMPLETE OCCLUSION IN THE PATHOGENESIS OF CEREBRAL SOFTENING. C. FOIX, J. A. CHAVANY and BASCOURET, Rev. neurol. **2**:77 (July) 1925.

The authors bring forward the possibility of cerebral softening occurring independently of complete arterial occlusion. Histologic examination of the involved blood vessels in the case reported reveals an evident chronic lesion of the vessel walls but no occlusion. It is then suggested that in addition to the arteritis, some outside factors must have entered into action: possibly an arterial spasm or a fall of arterial pressure, which, as already stated by Vincent, may follow a hemorrhage, or at least a change in the coagulation power and viscosity of the blood. Although these possibilities are mentioned, the only one already proved is arterial spasm, which is demonstrated by the strokes that occur sometimes during a hemicranic attack. The authors conclude that

cerebral softening may not correspond absolutely to a complete arterial occlusion.

In the discussion that followed, C. Vincent emphasized the possibility (sustained by two new cases) that a prolonged fall in blood pressure may lead to the production of a cerebral infarct, without any necessary pathologic involvement of the arterial walls. This last assertion, however, was objected to by Sicard.

FERRARO, Washington, D. C.

EPILEPSY AS A SYMPTOM OF DISSEMINATED SCLEROSIS. S. A. KINNIER WILSON and HENRY J. MACBRIDE, J. Neurol. & Psychopath. **6**:91 (Aug.) 1925.

Attention is called to the rarity of reports in the literature of the association of epilepsy or epileptiform attacks with disseminated sclerosis. The authors were able to collect eight cases to which they add seven of their own. In two of their cases the disease began with generalized epilepsy and local convulsions, definite symptoms of disseminated sclerosis appearing considerably later. As the disease progressed the general seizures diminished and only jacksonian attacks occurred. The other five cases are examples of the appearance of generalized epileptic seizures in the course of the disease; in some, these have been the first symptom and have preceded by years the appearance of the disseminated symptoms; in others, the course of the disease has been marked at intervals by the development of epileptic fits. As to the pathogenesis of these attacks, the authors postulate for the jacksonian fits an underlying cortical alteration and assume that this is constituted by some encephalitic patch. They compare the occurrence of general epileptic fits as an initial or early symptom of disseminated sclerosis with general seizures taking place as a prodromal manifestation of cerebral tumor, and point out that the pathogenesis of fits is not understood in either condition. In conclusion the authors state, "Epileptiform or epileptic seizures must be accepted definitely as occasional symptoms of disseminated sclerosis, and in this respect the disease falls in line with other cerebral toxi-infective states."

STACK, Milwaukee.

IMITATIVE HOMOLATERAL SYNKINESIS. HEMIANESTHESIA. PROBABLE THALAMIC LESION. C. VINCENT KREBS and MEIGNANT, Rev. neurol. **2**:202 (July) 1925.

The authors describe a man, aged 69, who after a slight ictus showed a right hemiparesis with predominant faciobrachial involvement. There were also right hemianesthesia to all kinds of stimuli except to the painful; and no spontaneous pain. On the affected side there was an unusual involuntary movement of the upper extremity imitating the voluntary movement of the lower extremity, and reciprocally. The authors think that the thalamus may be the seat of the lesion; such intense anesthesia associated with a slight motor paresis and without speech defect is ordinarily connected with a lesion of the thalamus. The involuntary movements differed somewhat from ordinary synkinesis; they appeared in fact in a nonparalyzed extremity showing no contracture and are not produced by a movement of the opposite extremity. They propose to call the movements observed imitative homolateral synkinesis.

The case described, as well as those described by Hillemand in his thesis, shows that paralysis and contracture do not necessarily accompany this kind of synkinesis, and that a certain amount of preserved motility is necessary to elicit it. The classic synkinesis of Marie and Foix may or may not coexist with the homolateral imitative synkinesis.

FERRARO, Washington, D. C.

ROENTGEN THERAPY OF TUMORS OF THE INFUNDIBULOHYPOPHYSIAL REGION. ROUSSY, BOLLACK, LABORDE and LEVY, Rev. neurol. **2**:297, 1924.

Within the past two and a half years the authors have treated eight tumors of the infundibulohypophysial region. The dosage used was 200,000 volts, 4.8 milliamperes, spark gap 41 cm. filters 0.5 mm. zinc and 2.0 mm. aluminum; distance 30 cm. area 10 cm.; application in three places, lateral and median frontal; dosage 4,000 to 4,500 R.

The case histories are given in some detail. One was a typical acromegaly with polyuria and visual disturbance; the polyuria diminished while the visual disorder remained stationary. Two cases of adiposogenital dystrophy in women were treated, both with normal sellas. In one the process was apparently arrested; in the other there was symptomatic cure. Of two similar but less advanced cases, one showed complete remission lasting several months, with later return and rapid progress of the disease; the other showed no beneficial results. Three cases of chiasmal lesions without other signs showed no therapeutic effect in one case, but very good results in the other two.

In comparison with results obtained in the irradiation of tumors of the brain, the success in these cases was marked and the roentgen ray proved an effective method of treatment.

FREEMAN, Washington, D. C.

THE ANATOMIC BASIS OF DECEREBRATE RIGIDITY. N. ZYLBERLAST-ZAND, Rev. neurol. **1**:998 (June) 1925.

Having recalled the careful experiments of Rademaker which proved irrefutably that the red nucleus presides over the regulation of the normal tonus of the body, the author, on the basis of the experiments by Sherrington, Horsley, Magnus and Thiele which prove that the cerebellum is not the center of decerebrate rigidity, expresses the view that this center must be sought in the medulla oblongata below the level of entry of the eighth cranial nerves. Transection of the brain stem at this level produces flaccidity of the rigid muscles almost every time. In an attempt to find the center for decerebrate rigidity, the author recalls the Hunter experiments which have shown that Deiter's nucleus has no influence on decerebrate rigidity. A method of injuring the olivary bodies is then described and the results of the experiments are reported. In two cases, section of the olive on one side led to disappearance of the rigidity on both sides. In another case, destruction of one olive was followed by flaccidity of the rigid muscles on the same side. The author calls attention to these results without making, however, any definite statement on the importance of the olivary formations in decerebrate rigidity.

FERRARO, Washington, D. C.

RESULTS SIXTEEN YEARS AFTER SPINAL ACCESSORY AND FACIAL ANASTOMOSIS. LECOUTURIER, Franco-Belgian Arch. Surg. **28**: (April) 1925.

The patient had a complete left facial paralysis following cranial trauma. The left spinal accessory nerve was therefore severed and an anastomosis made with the facial. The result, sixteen years after anastomosis, is not particularly satisfactory. In repose there is a return of facial symmetry, and the muscular tone on the operated side is fair. But there is no return of voluntary motion. The patient cannot close his left eye, whistle or elevate the left corner of his mouth. There is only very slight return of the normal skin wrinkles in the left half of the face. He can hold liquids in his mouth, which he could not do prior to the nerve suture. When he moves his left shoulder there is a

marked left facial spasm with closure of the eye and elevation of the corner of the mouth. There is, however, absolutely no return of coordinated facial movements. The author believes that the spinal accessory is not the best nerve to use for facial anastomosis as reeducation of facial movements is difficult. He believes the hypoglossal is the nerve of choice.

GRANT, Philadelphia.

CESSATION OF THE EPILEPTIC FIT AFTER INTRAVENOUS INJECTION OF CALCIUM CHLORIDE AND FAVORABLE RESULTS OF SUCH TREATMENT IN EPILEPSY. M. PETZETAKIS, Rev. neurol. **2**:174 (July) 1925.

The author reports two cases of essential epilepsy treated for several months by means of intravenous injections of calcium chloride. During the first month 0.5 Gm. was given each two days. In the second month the dose was raised to 0.8 Gm., and in the third lowered again to 0.5 Gm. During the fourth month two injections of 0.8 Gm. were given weekly. The course in both cases was favorably influenced by this treatment. In the first case, when an injection was made during a seizure, the fit stopped after one minute, the ordinary duration of the attacks being from ten to fifteen minutes. Later, the calcium treatment led to disappearance of the fits which had usually appeared each month. In the second case, during the fourth month the patient, who usually had a monthly fit and two vertigo attacks, had only one short fit after the second month of treatment.

FERRARO, Washington, D. C.

SYRINGOMYELIA IN ASSOCIATION WITH ACROMEGALY. HENRY J. MACBRIDE, J. Neurol. & Psychopath. **6**:114 (Aug.) 1925.

Two clear-cut cases are reported in each of which acromegaly and syringomyelia were very pronounced. In reviewing cases from the literature, the author questions whether some were true acromegaly. In both of the author's cases the acromegalic symptoms appeared first; if any relationship is to be presumed between the two conditions, it is the author's belief that one must place syringomyelia as secondary to, or as a complication of, the acromegaly. Attention is called to cases in the literature in which changes around the central canal in acromegaly have been found at necropsy, and the conjecture is brought forward that, in view of the rather frequent occurrence of splanchnomegaly with increase in size of the organs due to hyperplasia of the functional cells and ultimate fibrosis, a similar action may take place in the spinal cord in connection with the ependymal cells of the central canal and ultimate gliosis.

STACK, Milwaukee.

NERVE ANASTOMOSIS IN PARALYSIS OF VOCAL CORD. L. COLLEDGE, Brit. M. J. **1**:547 (March 21) 1925.

Colledge in describing a series of experiments on nerve anastomosis in vocal cord paralysis concludes from his experiments that: although a nerve connection may be reestablished by recurrent laryngeal vagus anastomosis, it is useless to expect return of spontaneous movement in the corresponding vocal cord. In anastomosis with a descendens noni, tension was restored in the paralyzed cord, but there was no spontaneous movement. In anastomosis of the phrenic nerve, spontaneous movement can be restored to the vocal cord.

POTTER, Akron, Ohio.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

Regular Meeting, Oct. 23, 1925

SHERMAN F. GILPIN, M.D., *President, in the Chair*

CHRONIC ANTERIOR POLIOMYELITIS DEVELOPING AFTER TRAUMA. DR. S. F. GILPIN.

This case is presented because of the close association of the injuries received with the chronic muscular atrophy which is now present. A man, aged 57, gives a history of good health until July, 1923, when he was injured. He was assaulted by a man who tripped and threw him, and then "kneed" him in the back. He was able to get on his feet, leave the house in which he was working and get to the street; then because of weakness he was compelled to sit down to rest. He went home and to bed and was under the care of a physician for several days. He vomited a number of times shortly after the injury. He has not been able to work since the trauma and was allowed thirteen weeks' compensation. He complained of weakness in the left leg and arm during this time and since. At the termination of the compensation period he was considered cured in spite of his statement about his left arm and leg. He believes his right leg is normal but his right shoulder is weak.

The pupils, tongue, cranial nerves, sensation, station and laboratory examinations are normal. He walks with a limp of the left leg. The knee jerks are slightly increased. The grip in the left hand is weak, in the right hand good. Atrophy of the muscles is present in the left hand and forearm, and there is considerable atrophy of the muscles about the shoulders, more marked on the right. The left leg is weak and quickly tires. There appears to be some atrophy of the left gluteal muscles although no fibrillary contractions have been noticed. The electrical examination of the atrophied muscles shows a quantitative loss in reaction.

Active treatment with electricity, massage and increasing doses of strychnia has been given, but no improvement has occurred. The patient himself thinks he is becoming weaker and that the right hand is not as strong as formerly. Whether the atrophy is increasing I am unable to say at this time.

TEMPORARY TONIC SPASM OF THE SUPERIOR RECTI MUSCLES ASSOCIATED WITH THE PARKINSONIAN SYNDROME AS A SEQUEL OF EPIDEMIC ENCEPHALITIS. DR. ALFRED GORDON.

CASE 1.—A man, aged 23, had a typical attack of epidemic encephalitis in 1921, which was followed by a parkinsonian state, with right hemiparesis and excessive salivation. The unusual symptom in this case is the occurrence of a sudden tonic spasm of both superior recti which may last from a few minutes to several hours; it is characterized by a conjugate upward movement of the eyes with fixation. On several occasions the patient observed that in an attempt to look upward a similar spasm occurred. During the period of fixation he suffers great discomfort. The lesion is probably an irritative one in those portions of the nuclei of the third nerves which innervate the recti muscles.

CASE 2.—A woman, aged 25, went through a severe attack of encephalitis. At present she shows a decided weakness of the left arm, but there are no changes in the reflexes. She has various manifestations referable to the vagosympathetic system. There is also a masklike face and some hypertonia in the brachiocervical muscles. The eyes are normal as to their fundi; but there occurs at intervals a spasmodic contraction of the ocular muscles which directs, with great force and tension, the eye-globes to the left, upper external angles of the orbits for a period of from one to twenty-five minutes. The nuclei of the fourth nerves are probably involved in the same manner as in the first case.

The literature abounds with descriptions of various paralytic ocular manifestations but contains few cases with spasmodic phenomena of the ocular muscles. The most recent article is by G. H. Benton in the *Journal of the Florida Medical Association*, July 12, 1925. Temporary paresis of the levator palpebrae muscle, toward the end of the day, has been observed. Bériel, of Lyon, observed a similar phenomenon of the ocular muscles. When the eyes are rotated to an extreme position, the musculature more or less rapidly becomes fatigued, and in spite of the patient's effort the eye-globes return to the normal position.

DISCUSSION

DR. WARREN SNYDER REESE: I am especially interested in this case because I had one somewhat like it not long ago. It occurred in a man, aged 20, who had had sleeping sickness and exhibited the parkinsonian syndrome. He had paralysis of downward movement and of convergence of both eyes and bilateral paresis of accommodation. In practically all the cases I have seen there is a decided weakness of convergence. A peculiarity is that these patients do not complain of diplopia, although they usually give a history of its occurrence during the acute attack. A short time ago I looked up a case in which the history suggested a paralysis of divergence. This patient had been seen by an ophthalmologist who later told me that he did not believe that paralysis of divergence occurs; he considered that this patient had bilateral paresis of the external recti. I do not think these cases receive the attention they deserve; we should study them carefully and record our observations, as the mechanism of these conditions is very poorly understood. Several cases similar to those of Dr. Gordon were reported in the last issue of the *Journal of Ophthalmology*.

DR. CLARENCE PATTEN: In regard to the case which Dr. Reese mentioned, there was complete inability to move the eyes downward, as well as some weakness in associated upward movements. When the patient tipped his head backward, however, the eyes would come downward with a mechanical doll-like movement. This was to me a curious and interesting phenomenon, and I do not know how to explain it.

Less than a year ago, I saw, with Dr. Weisenburg, a patient with spasm of the eyelids. The eyes would close very tightly and resist any attempt to open them manually. The patient, however, by elevating his left brow with his hand and continuing the pressure, could produce after a time a slow upward movement of the left lid. In a little while the right lid would also elevate slowly. This spasm of the eyelids occurred some months after an acute attack of encephalitis and at the time the patient was seen the condition was progressive.

DR. CHARLES S. POTTS: Hohman, in the *Journal of the American Medical Association*, May 16, 1925, reported at least two cases of this sort. He also called attention in this article to the fact that these cases of spasmodic upward

movement have been in the past considered by ophthalmologists to be due to hysteria. For this reason I think they have practical importance. Other symptoms of encephalitis may also be mistaken for hysteria. At this time, when the sequelae of encephalitis are becoming more frequent, it is important to be on guard in order not to make mistakes in diagnosis.

A Case of Thermalgia (Causalgia). Dr. Frederic H. Leavitt.

This patient is of interest in that she presents an unusual variety of neuralgia, in which pain is accompanied by an intense subjective sense of burning in the palms of both hands and excessive hyperidrosis. A digest of the literature reveals little material relative to this syndrome, with the exception of articles by Sir James Purves Stewart and John Stopford in which they describe the condition accurately. The characteristic burning pain is commonly associated with vasodilatation, redness and sweating of the affected area, generally of the palms of the hands or the soles of the feet. The condition is most prone to follow injury to the nerves or arteries of the affected limbs, but also may occur independently of trauma. The pain is likely to vary in intensity and becomes worse when the hand or foot is dry, and also when the temperature of the surrounding air is hot and humid. Thermalgia is considered to be due to reflex vasodilatation or to irritation of the peri-arterial sympathetic plexus of the main arteries, falling therefore into the group of diseases of which erythromelalgia, Raynaud's disease and intermittent claudication are examples.

The patient I am presenting is a white girl, single, aged 23, who has worked for several years as a stenographer, telegraph operator and clerk. About four years ago she became aware of a gradually increasing painful reddening of the palms of both hands, which would become much worse in hot, humid weather. During the last year there has been an aching pain in the center of the palms of both hands; these areas became pallid and surrounded by a circle of livid, bluish reddening of the skin. When the pain and reddening were most severe, there was excessive sweating of the palms. Neither the pain nor the discoloration seemed to be affected by holding the hands in an elevated position. She has never experienced similar pain in any other part of her body and there is no history of injury to the arms or of illness immediately preceding the onset of this condition. She has been a telegraph operator and was accustomed to use both arms and hands until they would become greatly fatigued. When this fatigue reaction would occur she noticed that the veins on the dorsum of each hand swelled and became painful and caused her great esthetic annoyance because of the disfigurement.

Physical examination reveals little that is abnormal with the exception of the condition of the hands which has been described. All tendon reflexes are normal and equal on the two sides, and the only sensory change is the thermal hyperalgesia of the palms of both hands. Blood pressure is 100 systolic, and 75 diastolic; heart rate, 100 per minute. The thyroid is slightly enlarged and the patient says that the swelling in her neck seems to be more noticeable when the condition of her hands is better; when the thyroid decreases in size, the pain in the hands tends to become worse. She presents no other symptoms suggestive of hyperthyroidism. The possibility of cervical ribs was considered, but a roentgenogram was negative for this condition. Serology, blood count and urinalysis are normal.

No other member of the family has had a comparable condition as far as known. One brother has idiopathic epilepsy.

During the past summer the patient has been treated by the administration of iodine and thyroid extract, and she reports that the pain, sweating and discoloration have been much less annoying.

DISCUSSION

Dr. Charles M. Byrnes: I have reviewed this subject rather thoroughly in Tice's Practice of Medicine, and from that study I am quite certain that causalgia was first described by Dr. Weir Mitchell. The case presented by Dr. Leavitt appears to me to resemble erythromelalgia more than causalgia. Causalgia is associated with incomplete nerve injuries, particularly those affecting the median nerve, and sometimes those involving the ulnar or sciatic nerves. It is interesting to note that causalgia and tic douloureux are strikingly similar in some aspects. Both are characterized, at times, by vasomotor disturbances, paroxysmal sharp attacks of pain and trigger zones. Instances were described during the World War in which causalgia attacks were induced in the injured arm by peripheral irritation of the opposite hand. It would be interesting to know whether or not Dr. Leavitt observed in his patient any sclerosis of the palpable blood vessels, or whether or not elevation of the arms caused any appreciable change in pulse pressure.

Dr. Frederic H. Leavitt: Her[a] peripheral arteries are not particularly palpable. The color of the hands, the subjective sense of pain and the pulse pressure were not altered by changing the position of the arms. This condition is described by the French and British writers as "thermalgia." It was first reported by Dr. Weir Mitchell, and it differs quite materially from the classic textbook pictures of erythromelalgia. The rather interesting feature of this case is the change in the size of the thyroid. When this gland is quite noticeably swollen she has practically no pain and no redness to speak of, and when this subsides, the reverse condition ensues. It was because of this fact that I administered thyroid extract.

A Case of Paralysis Agitans with Hysteria. Dr. B. P. Weiss.

A Russian man, aged 51, a tailor, had pulmonary tuberculosis about 1920 and was in a sanatorium for one year; that condition is now quiescent. He said that there was no venereal infection. About one and one-half years ago he noticed weakness and stiffness in his legs and numbness in his limbs. Nine months ago he observed a tremor of his right hand; this symptom became more marked, progressing to the arm. Recently he has had "spells," in which he felt dizzy and the head became "light"; he then emitted a peculiar noise or whistling sound, and the tremor involved the entire body; his breathing became rapid and irregular and was followed by relaxation, but without loss of consciousness. There was no biting of the tongue, frothing of the mouth, nor sphincter disturbance. He has had from one to six attacks in twenty-four hours, all diurnal.

On examination, the facies is parkinsonian; the gait is slow and somewhat spastic, and there is loss of associated automatic movements. The pupils are irregular, and reaction to light is sluggish, although they respond well in accommodation. The eyegrounds and cranial nerves are normal. The right arm is more spastic than the left, and the right hand presents a pill-rolling tremor. There is a glovelike anesthesia of the right arm. Both legs are spastic, the right more than the left; all the reflexes are hyperactive, without Babinski's sign or ankle clonus. Although this man presents Argyll-Robertson

pupils, his serology and spinal fluid are negative. His mentality is fair and the memory is uninvolved, but cerebration is rather slow. There is no defect of speech. He is quite emotional, giving vent to frequent crying spells; these attacks appear to be entirely functional and can be induced by suggestion. This case appears to be one of paralysis agitans with superimposed hysteria.

DISCUSSION

Dr. Charles M. Byrnes: I am interested in the occurrence of this syndrome in a case of paralysis agitans associated with syphilis. The association of the two diseases is extremely rare, and it will be interesting to know in how many cases of paralysis agitans Dr. Weiss has been able to demonstrate the presence of syphilis.

Dr. B. P. Weiss: My recollection is that I have had one or two cases of paralysis agitans with syphilis at Blockley. Whether syphilis was the causative factor, I am unable to say, but there was a positive blood serology.

The Newer Staining Methods as Applied to Neuropathology. Dr. N. W. Winkelman.

Lantern slides were shown illustrating the newer stains, such as the gold sublimate method of Cajal, in normal brains, in Huntington's chorea and in general paralysis; also Hortega's microglia stain in the same conditions. The appearance of senile plaques in the Hortega method was pointed out. Klarfield's modification of the tannin silver stain of Ranke was also shown, and its rôle in the differentiation of gumma from tuberculoma was stressed. The iron stain, with special reference to its increase in general paralysis, was shown. It was felt, as pointed out by Jakob, that by means of the iron and the Hortega stains a diagnosis of general paralysis could be made.

Book Reviews

ADDRESSES TO MENTAL NURSES. Edited and Arranged by DR. BEDFORD PIERCE. Price, 7 shillings, 6 pence net. Pp. 288. London: Baillière, Tindall & Cox, 1925.

One sometimes wonders if anything new can be said to nurses in the line of ethical admonition and idealism. In this volume many of the best things are said in the best way. A touch of personality is added by the short biographical sketch of each author, which lends strength to the desired impression. While these addresses were delivered to nurses engaged in the care of mental patients and apply directly to the problems of this special line of nursing, they contain much that is particularly applicable to all general nursing, because of the importance, constantly insisted on, of nursing the patient rather than the case.

The volume is a selection of excellent talks by persons most competent to give them. They do not fail to inspire the reader with the seriousness and responsibilities of the nurse's work among mental patients, and especially with the curative power which a nurse with character, refinement and poise may exert. While there is no particular sequence to the lectures, they individually, and as a whole, stimulate the nurse to thoughtful interest in her work, to resourcefulness in dealing with patients and to a personal interest, which never allows one to give up hopeful effort in discouraging situations. The book abounds in practical and scientific facts which help the nurse in understanding her patient and give her an approach to her work which is so essential to success in this branch of nursing.

LA MÉLANCHOLIE: CLINIQUE ET THÉRAPEUTIQUE. BY R. BENON. Price, 10 francs. Paper. Pp. 154. Paris: Gaston Doin, 1925.

The author endeavors to establish that there is a "true melancholia," recoverable in 60 per cent of the cases, which should be distinguished from manic-depressive depression and from the states of depression that occur as symptoms in other diseases. He protests as a "gross error of clinical observation" the confusion of states of depression with melancholia as has been done by Kraepelin in his manic-depressive psychoses. The essential feature of "true melancholia," acording to Benon, lies in the etiology. It arises on the basis of adequately motivated painful emotion or grief (chagrin); the result of some misfortune, some loss, or some cause for shame. Among contributing factors are the menopause (the age of predilection for the development of the disease), senile changes, autointoxications, etc.; predisposing factors are to be found in heredity.

Clinically, the condition is an emotional disorder, "a form of acquired dysthymia, or, better, of hyperthymia on the basis of some grief." Asthenic symptoms are progressive, secondary and proportional to the emotional pain, whereas in periodic depressions the asthenia is primary and remains practically constant throughout the attack. Melancholia is accompanied by delusions that interpret the emotion, are self-accusative in type and systematized. The mental picture may be complicated by ideas of persecution, hypochondria, excitement or dementia praecox, doubtless as the result of acquired or congenital predispositions. Confusional symptoms and dementia may coexist as the result of complicating intoxication or senile changes. The disease is frequently curable

even after lasting for months or years, and there is very little tendency to recurrence. Two types are distinguished as major and minor melancholia, which represent merely different degrees of severity.

The principal interest of the book, however, lies in the purpose with which it was written. Dr. Benon deplores the neglect of a true psychiatry and the tendency to concentrate attention on structural changes. He is careful to point out that he fully appreciates the value and importance of this latter aspect of mental disorders, but he insists that failure to study the psychic aspect results not only in faulty diagnoses but also in neglect of psychotherapy and a lowered standard of care for patients in hospitals. Research in the fields of anatomy, pathology and biology should be pushed with the utmost vigor, but there is still need for the psychiatric approach.

LES TUMEURS DU CERVEAU, WITH A PREFACE BY PROF. PIERRE MARIE. By PROF. VIGGO CHRISTIANSEN, Physician in charge of the Royal Hospital of Denmark, Member of the Academy of Medicine of Paris. Second Edition published with the cooperation of Dr. Édmond Terris. Pp. 398. Paris: Masson & Cie, 1925.

The first edition of this book appeared in 1917 and consequently needed, and has received, "radical revision." This relates especially to tumors involving the chiasm, to the often confusing picture of chronic epidemic encephalitis and to operative results. The work is essentially clinical and is in the form of twelve lectures: three on tumors of the motor region, two on tumors of the cerebellopontile angle and one each on those of the occipital lobes, of the base of the brain, of the cranial base, of the chiasmic region and of the cerebellum and pons. Then a chapter (lecture) on the uncertainties of diagnosis, and one on surgical treatment. From the foregoing it will be seen that the subject is approached along the line of localization. This mode has its practical value but makes systematic treatment of the subject difficult or impossible and necessarily involves considerable repetition.

But this repetition is not altogether undesirable. Obviously these lectures are designed for a general medical audience and in such circumstance the repetition of a principle or of some important neurologic fact viewed under different conditions is most useful. Though the lectures are somewhat rambling and at times a bit diffuse, they are eminently practical and richly illustrated by actual cases, and their interest is enhanced by the ever present stamp of individuality. Other authors are duly considered and given credit, but this book is essentially a presentation of the exceptionally large experience of the author, of his methods and of his views. His views are sound and his methods good. The case reports with the attendant discussion of symptoms and diagnosis constitute the most valuable feature of the book. They give the reader a clear picture of the various phases of brain tumor and constitute an excellent clinical course on a difficult subject.

The chapter on surgical treatment is rather a discussion of the indications and contraindications for such treatment. It is a masterly discussion and a reasonable one. Among other things the author recognizes that the ability and equipment of the operator are vital elements in a decision for or against operation.

A book of this character needs a first rate index. The index presented is unusually good for a continental work: but it could be better.

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